Integrated disease management interventions for patients with chronic obstructive pulmonary disease (Review)

Kruis AL, Smidt N, Assendelft WJJ, Gussekloo J, Boland MRS, Rutten-van Mölken M, Chavannes NH

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[Intervention Review]

Integrated disease management interventions for patients with chronic obstructive pulmonary disease

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ABSTRACT

Background

In people with chronic obstructive pulmonary disease (COPD) there is considerable variation in symptoms, limitations and well-being, which often complicates medical care. To improve quality of life (QoL) and exercise tolerance, while reducing the number of exacerbations, a multidisciplinary program including different elements of care is needed.

Objectives

To evaluate the effects of integrated disease management (IDM) programs or interventions in people with COPD on health-related QoL, exercise tolerance and number of exacerbations.

Search methods

We searched the Cochrane Airways Group Register of trials, CENTRAL, MEDLINE, EMBASE and CINAHL for potentially eligible studies (last searched 12 April 2012).

Selection criteria

Randomized controlled trials evaluating IDM programs for COPD compared with controls were included. Included interventions consisted of multidisciplinary (two or more health care providers) and multi-treatment (two or more components) IDM programs with a duration of at least three months.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data; if required, we contacted authors for additional data. We performed meta-analyses using random-effects modeling. We carried out sensitivity analysis for allocation concealment, blinding of outcome assessment, study design and intention-to-treat analysis.

Main results

A total of 26 trials involving 2997 people were included, with a follow-up ranging from 3 to 24 months. Studies were conducted in 11 different countries. The mean age of the included participants was 68 years, 68% were male and the mean forced expiratory volume in one second (FEV1)% predicted value was 44.3% (range 28% to 66%). Participants were treated in all types of healthcare settings: primary (n = 8), secondary (n = 12), tertiary care (n = 1), and in both primary and secondary care (n = 5). Overall, the studies were of high to moderate methodological quality.

Compared with controls, IDM showed a statistically and clinically significant improvement in disease-specific QoL on all domains of the Chronic Respiratory Questionnaire after 12 months: dyspnea (mean difference (MD) 1.02; 95% confidence interval (CI) 0.67 to 1.36); fatigue (MD 0.82; 95% CI 0.46 to 1.17); emotional (MD 0.61; 95% CI 0.26 to 0.95) and mastery (MD 0.75; 95% CI 0.38 to 1.12). The St. George's Respiratory Questionnaire (SGRQ) for QoL reached the clinically relevant difference of four units only for the impact domain (MD -4.04; 95% CI -5.96 to -2.11, P < 0.0001). IDM showed a significantly improved disease-specific QoL on the activity domain of the SGRQ: MD -2.70 (95% CI -4.84 to -0.55, P = 0.01). There was no significant difference on the symptom domain of the SGRQ: MD -2.39 (95% CI -5.31 to 0.53, P = 0.11). According to the GRADE approach, quality of evidence on the SGRQ was scored as high quality, and on the CRQ as moderate quality evidence. Participants treated with an IDM program had a clinically relevant improvement in six-minute walking distance of 43.86 meters compared with controls after 12 months (95% CI 21.83 to 65.89; P < 0.001, moderate quality). There was a reduction in the number of participants with one or more hospital admissions over three to 12 months from 27 per 100 participants in the control group to 20 (95% CI 15 to 27) per 100 participants in the IDM group (OR 0.68; 95% CI 0.47 to 0.99, P = 0.04; number needed to treat = 15). Hospitalization days were significantly lower in the IDM group compared with controls after 12 months (MD -3.78 days; 95% CI -5.90 to -1.67, P < 0.001). Admissions and hospital days were graded as high quality evidence. No adverse effects were reported in the intervention group. No difference between groups was found on mortality (OR 0.96; 95%CI 0.52 to 1.74). There was insufficient evidence to refute or confirm the long term effectiveness of IDM.

Authors' conclusions

In these COPD participants, IDM not only improved disease-specific QoL and exercise capacity, but also reduced hospital admissions and hospital days per person.

PLAIN LANGUAGE SUMMARY

Integrated disease management for chronic obstructive pulmonary disease

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory (lung), disabling disease which affects a lot of people worldwide and causes millions of deaths every year. People with COPD suffer differing levels of impairment, daily complaints/symptoms and number of exacerbations.

Different health care providers, such as doctors, nurses and physiotherapists, typically provide different components of care (for example medication, self management and education, exercise training) to people with COPD. The aim of an integrated disease management (IDM) program is to establish a program of different components of care in which different health care providers are co-operating and collaborating to provide efficient and good quality care.

Review question

We wished to determine the effect of such a program on quality of life, exercise tolerance and the number of exacerbations. We have chosen these outcomes as they are most important for people with COPD.

What we found

We evaluated 26 studies in 2997 people with COPD. Overall the evidence found was of high to moderate quality. The trials were conducted in 11 different countries. The average age of participants was 68 years, 68% of participants were men and the severity of COPD on average was severe (according to lung function measures). Some of the trials took place in GP clinics and some in hospitals. Overall, the studies were of good to moderate methodological quality.

People who participated in an IDM program had better quality of life and improved their exercise tolerance after 12 months. Furthermore, in participants treated with such a program, the number of hospital admissions related to exacerbations decreased and the total number of hospital days was reduced by three days. We found no evidence of an effect on mortality.

The results support an IDM program for people with COPD to optimize quality of life and exercise tolerance.

This plain language summary is up-to-date as of April 2012.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Integrated disease management compared to control for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: 8 studies in primary care, 12 studies in secondary care, 1 study in tertiary care, 5 studies in both primary and secondary care
Intervention: integrated disease management
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Disease management				
Quality of life measured on the SGRQ (St George's Respiratory Questionnaire) total score. Scale from: 0 to 100. Lower score indicates improvement Follow-up: 3 to 12 months	The mean change in the SGRQ (total score) ranged from 3.4 lower to 6.24 higher	The mean SGRQ (total score) in the intervention groups was **3.71 lower** (5.83 to 1.59 lower)	**MD -3.71** (-5.83 to -1.59)	1425 (13 studies)	⊕⊕⊕⊕ **high**[2]	MCID = -4 points, lower score means improvement
Quality of life measured on the CRQ dyspnoea domain Scale from: 0 to 7. Higher score indicates improvement Follow-up: 3 to 12 months	The mean change in the CRQ (dyspnoea domain) ranged from 0 to 0.2 lower	The mean CRQ dyspnoea domain in the intervention groups was **1.02 higher** (0.67 to 1.36 higher)	**MD 1.02** (0.67 to 1.36)	160 (4 studies)	⊕⊕⊕◯ **moderate**[1]	MCID = 0.5 points Results on the other domains of the CRQ (fatigue, emotion, mastery) were also all statistically and clinically relevant

Functional exercise capacity 6-minute walking distance (6MWD) Follow-up: 3 to 12 months	The mean change in the 6MWD ranged from 38 lower to 36 higher	The mean functional exercise capacity in the intervention groups was **43.86 higher** (21.83 to 65.89 higher)	**MD 43.86** (21.83 to 65.89)	838 (14 studies)	⊕⊕⊕○ **moderate**[3]	MCID = 35 meters. Sensitivity analysis did show there was inconsistency in the effect. After removing low-quality studies, the MD was 15.15 meters (95% CI 6.37 to 23.93, P <0.001)
Respiratory-related hospital admissions Follow-up: 3 to 12 months	**27 per 100**	**20 per 100** (15 to 27)	**OR 0.68** (0.47 to 0.99)	1470 (7 studies)	⊕⊕⊕⊕ **high**	
Hospital days per patient (all causes) Follow-up: 3 to 12 months	The mean change in hospital days ranged from 1.6 to 11.9 higher	The mean number of hospital days per patient (all causes) in the intervention groups was **3.78 lower** (5.9 to 1.67 lower)	**MD -3.78** (-5.9 to -1.67)	741 (6 studies)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IDM**: integrated disease management; **MCID**: minimal clinically important difference; MD: mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded one as there was considerable risk of bias in two studies on allocation concealment and two studies did not blind the outcome assessor.
[2]We did not downgrade due to risk of bias, as studies contributing more than 2.7% to the meta-analysis had a low risk of bias. Sensitivity analysis on high-risk studies did not change the effect or significance of the effect.
[3]We downgraded one as all included studies were of moderate to low quality. If we removed studies which had high or unclear risk of bias on allocation concealment, the effect decreased to 15 meters.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, systemic condition characterized by restricted airflow which is not fully reversible. It is a major cause of morbidity, due to the ageing of the world's population and the continued use of tobacco and exposure to indoor biomass pollution. The prevalence of COPD is expected to increase substantially in the coming decades (Lopez 2006; GOLD 2009). According to the World Health Organization (WHO), COPD will be the third leading cause of death in 2020 (Lopez 2006; WHO 2008). Given the rise in prevalence, COPD has important financial consequences, with high reported direct costs (healthcare resources, medication prescriptions) and indirect costs (absence from paid work, consequences of disability) (Britton 2003).

Optimal management of COPD is complex, as it is a multi-component disease. Clinical, functional and radiological presentation varies greatly from patient to patient, despite having a similar degree of airflow limitation (Wedzicha 2000; GOLD 2009; Agusti 2010). Evidence suggests that the previous 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of disease severity, solely based upon the degree of airflow limitation, is a poor predictor of other important negative features of COPD (Agusti 2010; Burgel 2010).

Health-related quality of life (HRQoL) and exercise tolerance may be more important to people with COPD than the more traditional measure of lung function. This is because COPD has a profound impact on HRQoL and exercise tolerance, even in those with modest airflow limitation (Engstrom 1996). Furthermore, impaired HRQoL (Domingo-Salvany 2002; Fan 2002; Martinez 2006) and exercise tolerance (Gerardi 1996; Pinto-Plata 2004) have been associated with an increased risk of mortality (Cote 2009).

In addition, some people are more prone than others to episodes of acute exacerbations, which are an important cause of morbidity, mortality, hospital admission and impaired health status (Seemungal 1998; Wedzicha 2000; Calverley 2003). Although exacerbations become more severe and occur more frequently with increased severity of COPD, this is not always the case. There is some evidence for a 'frequent-exacerbation' phenotype (or group of people) that exacerbate more often than would be expected given their 'severity' as predicted by lung function testing (Hurst 2010).

Episodes of exacerbations are often not reported by patients to health care providers (Seemungal 2000). An important reason for patients' delay in reporting an increase in symptoms to their doctor is the fear of being sent to hospital. This passive behavior can eventually lead to a respiratory crisis, indeed necessitating urgent referral. In order to break through the self reinforcing negative spiral of dyspnoea, deconditioning and social deprivation doctors need to collaborate with their patients, with a focus on self management skills: "if symptoms increase, you need to let us know rapidly to prevent further worsening" (Chavannes 2008). In viewing COPD as a disease process with a clinical, heterogeneous picture of progressive deterioration, an integrated system of care could be built on a disease management model. Ideally, it is based on active self management to slow down progression of the disease, including daily self care, patient-physician collaboration and exacerbation management. Information should be tailored to the person's needs, knowledge level and clinical profile and be accessible by the patient when they need it most (Tiep 1997; Bourbeau 2013).

Description of the intervention

In the last decade, the concept of integrated disease management (IDM) was introduced as a mean of improving quality and efficiency of care. IDM interventions are aimed at reducing symptoms and avoiding fragmentation of care, while containing costs. Therefore, IDM programs are generally believed to be cost-effective, but the available evidence is inconclusive. Several systematic reviews have shown positive results, at least for some outcomes of chronic IDM, in people with chronic heart failure (Gonseth 2004; Roccaforte 2005), diabetes (Norris 2002; Knight 2005; Pimouguet 2010) and depression (Badamgarav 2003; Neumeyer-Gromen 2004).

However, there is no consensus in the literature about the definition of IDM. Several definitions have been proposed since the introduction of the concept 'disease management'. In order to facilitate the communication between researchers, policy makers and IDM program leaders, Schrijvers proposed a definition, based on earlier reported definitions (Care Continuum Alliance; Dellby 1996; Epstein 1996; Ellrodt 1997; Zitter 1997; Weingarten 2002; Faxon 2004): "*Disease management consists of a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities. The goal of chronic disease management is to identify persons at risk for one or more chronic conditions, to promote self-management by patients and to address the illness or conditions with maximum clinical outcome, effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns*" (Schrijvers 2009). In addition, Peytremann-Bridevaux and Burnand added more elements, adapting the definition as follows: "*Chronic disease prevention and management consists of a group of coherent interventions, designed to prevent or manage one or more chronic conditions using a community wide, systematic and structured multidisciplinary approach potentially employing multiple treatment modalities. The goal of chronic disease prevention and management is to identify persons with one or more chronic conditions, to promote self-management by patients and to address the illness or conditions according to disease severity and patient needs and based on the best available evidence, maximizing clinical effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement*

patterns. Routine process and outcome measurements should allow feedback to all those involved, as well as to adapt the programme" (Peytremann-Bridevaux 2009).

How the intervention might work

There is great variation in the symptoms, functional limitations and degrees of psychological well-being of COPD patients, as well as the speed of the progression of COPD towards more severe stages (Agusti 2010). This calls for a multi-faceted response, including different elements (e.g. smoking cessation, physiotherapeutic reactivation, self management, optimal medication adherence) targeted at the patient, professional or organizational level. Therefore, IDM programs have been developed to improve effectiveness and economic efficiency of chronic care delivery (Norris 2003) by combining patient-related, professional-directed and organizational interventions (Wagner 2001; Lemmens 2009).

Why it is important to do this review

As health-related quality of life, exercise tolerance and number of exacerbations are the most important patient-related outcomes in COPD, the focus in this review will be on these primary outcomes. Several systematic reviews have been published that evaluated the effect of IDM in COPD patients (Adams 2007; Niesink 2007; Peytremann-Bridevaux 2008; Lemmens 2009; Steuten 2009). These reviews differ from our review in various ways. Adams' review focused solely on interventions which could be arranged according to the chronic care model of Wagner (Wagner 1996; Adams 2007). Furthermore, Adams included studies between 1966 and 2005. Since then, several studies focusing on IDM in COPD patients have been published. Niesink and colleagues evaluated the quality of life in COPD patients, but did not report outcomes of exacerbations or exercise tolerance. Furthermore, the authors decided not to perform a meta-analysis; reasons for this were not clearly described (Niesink 2007). Peytremann-Bridevaux performed a meta-analysis and focused on quality of life, exacerbations and exercise tolerance. However, they did not take into account the differences in study design (randomised controlled trials (RCT) versus before/after uncontrolled studies) in their conclusions (Peytremann-Bridevaux 2008). Lemmens' review examined the effectiveness of IDM in a mix of patients with COPD, asthma or both (Lemmens 2009). No subgroup analysis was performed for patients with COPD. Furthermore, conclusions were drawn irrespective of the study designs (i.e. RCTs, controlled clinical trials, quasi-experimental, controlled before and after time studies and time series designs; Lemmens 2009). Steuten et al aimed to determine the cost-effectiveness of COPD programs and the authors did not perform a meta-analysis of clinical effects (Steuten 2009).

Overall, all reviews suggested some beneficial effects on health status. However, firm conclusions could not be made regarding the effectiveness of IDM, due to the large heterogeneity in the interventions, study populations, outcome measurements and methodological quality. The literature searches of the aforementioned reviews for relevant RCTs investigating the effectiveness of IDM for patients with COPD were carried out between December 2006 and May 2008. Since then, several studies have been published. Furthermore, none of the former published systematic reviews were carried out according to the latest methods for conducting a systematic review (Higgins 2011). Within the framework of The Cochrane Collaboration, we have systematically and comprehensively evaluated the effectiveness of IDM in people with COPD.

OBJECTIVES

To evaluate the effectiveness of IDM programs or interventions in people with COPD on health-related quality of life, exercise tolerance and the number of exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) in which IDM programs or interventions were compared to controls in people with COPD. Cluster-randomized trials were also eligible. There were no restrictions regarding the language of the paper.

Types of participants

People with a clinical diagnosis of COPD according to the GOLD criteria were included: people having chronic respiratory symptoms (i.e. coughing, sputum or dyspnoea) and a limited post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of < 0.7. Severity of airflow obstruction was classified using the GOLD stages of 2009 (GOLD 2009). All GOLD stages were accepted. Studies including participants with other diagnoses than COPD were only eligible if the results of participants with COPD were available separately.

Types of interventions

We included studies where the IDM intervention consisted of strategies to improve the care for participants with COPD, including organizational, professional, patient-directed and financial interventions. We classified these according to the Cochrane

Effective Practice and Organization of Care Group (EPOC) taxonomy of interventions (EPOC 2008), complemented with patient-directed interventions (i.e. self management and education). Our definitive checklist consisted of the following components of the IDM intervention that could be scored:

1. Education/self management: i.e. education, self-management, personal goals and/or action plan, exacerbation management
2. Exercise: i.e. (home) exercise training and/or strength and/or endurance training
3. Psychosocial: cognitive behavioral therapy, stress management, other psychological assessment and/or treatment
4. Smoking cessation
5. Medication: optimal medication/prescription of medication adherence
6. Nutrition: dietary intervention
7. Follow-up and/or communication: structural follow-up and/or communication, case management by nurses, optimal diagnosis
8. Multidisciplinary team: active participation and formation of teams of professional caregivers from different disciplines, revision of professional roles, integration of services, local team meetings
9. Financial intervention: fees/payment/grants for providing IDM.

As IDM includes different components mentioned above, delivered by different healthcare disciplines, the RCT studies had to include:

1. at least two components of interventions as mentioned above;
2. active involvement of at least two different categories of healthcare providers; and
3. a minimum duration of the IDM intervention of three months.

In all studies, we determined the dominant component of the program.

We compared IDM versus controls (varying from usual care or no treatment to single interventions, mono-disciplinary interventions).

Types of outcome measures

Primary outcomes

1. Health-related quality of life (HRQoL), as reported by one of the following questionnaires: a validated disease-specific questionnaire, e.g. Clinical COPD Questionnaire (CCQ; van der Molen 2003; Kocks 2006), Chronic Respiratory Questionnaire (CRQ; Guyatt 1987), St. George's Respiratory Questionnaire (SGRQ; Jones 1991; Jones 2005), COPD Assessment Test (CAT; Jones 2009) or a generic questionnaire, e.g. Short Form-36 (SF-36; Ware 1992), Euro Qol-5D (EQ-5D; EuroQol Group 1990)).
2. Maximal or functional exercise capacity, as reported by one of the following outcomes: the peak capacity measured in the exercise laboratory using an incremental exercise test defined according to the results of timed walk tests e.g. 6- or 12-minute walk test (Redelmeier 1997) or shuttle run test (Singh 1992)).
3. Exacerbation-related outcomes, as reported by one of the following: time to first exacerbation, number of exacerbations, duration and/or severity, and measured by reporting of symptoms, antibiotics or prednisolone prescriptions and/or hospital admissions or hospital days related to exacerbations.

Secondary outcomes

Clinical outcomes

1. Dyspnea, as measured by the Medical Research Council (MRC) Dyspnea Scale (Bestall 1999) or Borg score (Borg 1970).
2. Survival (mortality).
3. Lung function (FEV1, FVC).
4. Depression, as measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983) or the Beck Depression Inventory (BDI) score (Beck 1961).

Process-related outcomes

1. Co-ordination of care, e.g. accessibility of care, participation rate in the disease management program, satisfaction of health care providers and participants with regard to the program, or the extent to which disease management was implemented, from the perspective of the patient (PACIC; Glasgow 2005) and the caregiver (Bonomi 2002).

We evaluated outcomes at the following endpoints: a) short-term (12 months or less); b) long-term (longer than 12 months) follow-up, if possible.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Register of trials, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE and CINAHL. The search was performed without language restrictions, using the highly sensitive Cochrane Collaboration search strategy, which aims to identify all randomised controlled trials (Lefebvre 2009). We used specific MeSH headings and additional keywords to identify all RCTs on IDM in COPD patients. As IDM programs were first described in 1990, our search was restricted to publications from 1990 onwards. The complete search strategies

for the database searches are provided in the appendices (MEDLINE Appendix 1; EMBASE Appendix 2; CINAHL Appendix 3; CENTRAL Appendix 4; Airways Register Appendix 5). The search has been conducted up to April 2012. We ran an update search on 12 April 2013, but the results have not been fully incorporated: nine studies have been added as 'ongoing studies' and three studies have been added as 'studies awaiting classification'.

Searching other resources

In order to identify all possible studies, we carried out an additional search for systematic reviews in the Cochrane Database of Systematic Reviews. We screened reference lists of included RCTs and systematic reviews for potential studies for this review. To identify ongoing or new studies, we searched databases of ongoing studies, including ClinicalTrials.gov and other relevant registers.

Data collection and analysis

Selection of studies

Two review authors (AK and NS) independently assessed the title and abstract of all identified citations. We excluded all trials that were not randomised controlled trials or in which participants had no diagnosis of COPD. All studies excluded by the first two review authors because of the nature of the intervention were double-checked by a third review author (NC). Furthermore, if there was any doubt, we retrieved the full-text article and examined it for inclusion eligibility. Disagreements were discussed in a consensus meeting.

Data extraction and management

We collected the following information from included studies in our review: 1) the study design (i.e. randomisation method, sample size, blinding); 2) participant characteristics (i.e. diagnosis COPD according to GOLD criteria, age, sex); 3) interventions (i.e. setting, number of professionals involved, elements of IDM program/intervention, frequency and duration of intervention); 4) outcome measures and timing of outcome assessment; 5) results (i.e. loss to follow-up, outcomes). The outcome data were extracted by one author (AK) and checked by another (NC) using a standardized data extraction form. In case of missing data, we contacted the authors of these studies for additional information or clarification.

Assessment of risk of bias in included studies

Two of us (AK and NC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), according to the following items:

1. Allocation sequence generation
2. Concealment of allocation
3. Blinding of participants and health care providers, in relation to the intervention
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting

As cluster-randomized trials were also considered for inclusion, we added the following design-related criteria for these types of studies:

1. Recruitment bias (i.e. individuals are recruited after the clusters have been randomised)
2. Baseline imbalance between groups (i.e. the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters)
3. Loss of follow-up of clusters (i.e. missing clusters and missing outcomes for individuals within clusters may lead to a risk of bias in cluster-randomized trials)
4. Methods of analysis adequate for cluster-randomized controlled trials (i.e. taking clustering into account in the analysis) (Higgins 2011)

We judged all items as high, low or unclear risk of bias. We resolved disagreements in a consensus meeting.

Measures of treatment effect

We analyzed the results of the studies using RevMan 5, using random-effects modeling. We used forest plots to compare results across trials. The results were related to the minimal clinically important difference (MCID).

We expressed the results of each RCT as risk ratios (RR) with corresponding 95% confidence intervals (95% CI) for dichotomous data, and mean difference (MD) or standardized mean difference (SMD) for continuous data, depending on the similarity of outcome measurement scale (i.e. MDs are used when all studies use the same outcome measurement scale and SMDs when studies use different outcome measurement scales). We summarized data in a meta-analysis only if the data are clinically and statistically sufficiently homogenous. If the meta-analysis led to statistically significant overall estimates, we transformed these results (pooled estimate of RR, MD or SMD) back into measures which are clinically useful in daily practice. We planned to use the number needed to treat for an additional beneficial outcome (NNTB) and the absolute and/or relative improvement on the original units in order to report these as the final results of the review.

Unit of analysis issues

In case of a unit of analysis error occurrence in cluster-randomized controlled trials, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). The effective sample size of a single intervention group in a cluster-randomized trial is its original sample size divided by a quantity called the 'design effect'. The design effect is 1+ (M-1)* ICC,

where M is the average cluster size and ICC is the intra-cluster correlation coefficient. For dichotomous data, both the number of participants and the number experiencing the event were divided by the design effect. For continuous data, only the sample sizes were reduced; means and standard deviations remained unchanged (Higgins 2011).

Dealing with missing data

In case of missing data, we planned to contact the authors for additional information about the missing data for individuals. We sent a reminder if we did not receive a response. Secondly, we planned to assume the missing values to have a poor outcome. For continuous outcomes (i.e. health-related quality of life, exercise capacity) and dichotomous outcomes (i.e. mortality), we planned to calculate the effect size (SMD, MD, RR) based on the number of participants analyzed at the time point. If the number of participants analyzed is not reported for each time point, we planned to use the number of randomised participants in each group at baseline. We planned to perform sensitivity analysis to investigate whether our assumptions have been reasonable (i.e. comparing results using number of participants analyzed with number of participants randomised).

Assessment of heterogeneity

We measured clinical and statistical heterogeneity using the I^2 statistic (Higgins 2011). A P value of less than 0.10 or an I^2 value greater than 50% indicates substantial heterogeneity. In case of heterogeneity, we assessed studies, if possible, with respect to:

1. control group: a) no treatment; b) treatment with one health care provider; c) treatment with one component; d) other disease management programs (short duration of therapies);
2. intervention group, with regard to a) type of health care providers (i.e. general practitioner, lung specialist, physiotherapist, practice nurse); b) different components as listed by the EPOC classification (EPOC 2008); c) frequency and duration of intervention.

In case of substantial heterogeneity, we explored the data further, including subgroup analyses (see Subgroup analysis and investigation of heterogeneity) in an attempt to explain the heterogeneity.

Assessment of reporting biases

In order to determine whether reporting bias was present, we evaluated whether the protocol for the RCT was published before recruitment of patients of the study was started. For studies published after 1 July 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch) (De Angelis 2004). For each study, we evaluated whether selective reporting of outcomes was present (outcome reporting bias). Furthermore, we made a funnel plot to assess the possibility of reporting bias.

Data synthesis

We pooled results of the studies using the random-effects model. For continuous data, we recorded the mean change from baseline to endpoint and standard deviation (SD) for each group. For dichotomous data we recorded the number of participants with each outcome event and calculated the odds ratio (OR). We used results reported at three months, as our predetermined inclusion criteria postulated a program of at least three months duration (to ensure sufficient impact). If data at three months were unavailable, we analyzed the data measured most closely to this time point. We evaluated outcomes at short- (3 to 12 months) and long-term (> 12 months) follow-up.

We presented the main results of the review in a 'Summary of findings' table, which includes an overall grading of the evidence using the GRADE approach in accordance with the recommendations laid out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This involves making separate ratings for quality of evidence for each patient-important outcome and identifies five factors that can lower the quality of evidence, including: study limitations; indirectness of evidence (also called clinical heterogeneity with regard to study population, intervention, control group and outcomes); unexplained heterogeneity or inconsistency of results (i.e. statistical heterogeneity); imprecision of results (i.e. due to small sample sizes and few events); and high probability of publication bias. However, other factors can increase the quality of evidence, such as large magnitude of effect; plausible confounding, which could reduce the demonstrated effect; and dose-response gradient (GRADE Working Group 2004). We presented the short- and long-term outcomes for our primary outcomes in the 'Summary of findings' table if possible.

Subgroup analysis and investigation of heterogeneity

In order to explain heterogeneity between the results of the included studies, we planned the following subgroup analyses a priori (where data were available) to determine if outcomes differed among:

1. patients with different severity of disease, according to GOLD stage (GOLD 2009) or MRC Dyspnea Scale (Bestall 1999) (e.g. patients with GOLD 1/2 versus GOLD 3/4, and/or patients with a MRC score 0 to 2 versus MRC 3 to 5);
2. the setting of the IDM intervention (e.g. primary, secondary or tertiary care);
3. design of the studies (individually randomised patients versus cluster-randomized patients (with and without adjusting for design effect));
4. control group: a) no treatment; b) treatment with one health care provider; c) treatment with one component; d) other disease management interventions (short duration of therapies);

5. intervention group, with regard to a) type of health care provider (i.e. general practitioner, lung specialist, physiotherapist, practice nurse); b) different components as listed by the EPOC classification (EPOC 2008); c) frequency and duration of intervention.

Sensitivity analysis

We carried out sensitivity analyses for the primary outcome measurements, in order to explore effect size differences and the robustness of conclusions. We planned sensitivity analysis determined a priori based on:

1. studies without study limitations with regard to a) allocation concealment; b) blinding of participants and investigators; c) recruitment bias; d) baseline imbalance between groups; e) loss of follow-up of clusters; f) adequate analysis;
2. method of analysis: a) results of studies using number of patients analyzed; b) studies using number of patients randomised.

We presented the main results of the review in a 'Summary of findings' table, which includes an overall grading of the evidence using the GRADE approach (GRADEpro; GRADE Working Group 2004) and a summary of the available data on the main outcomes, as described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

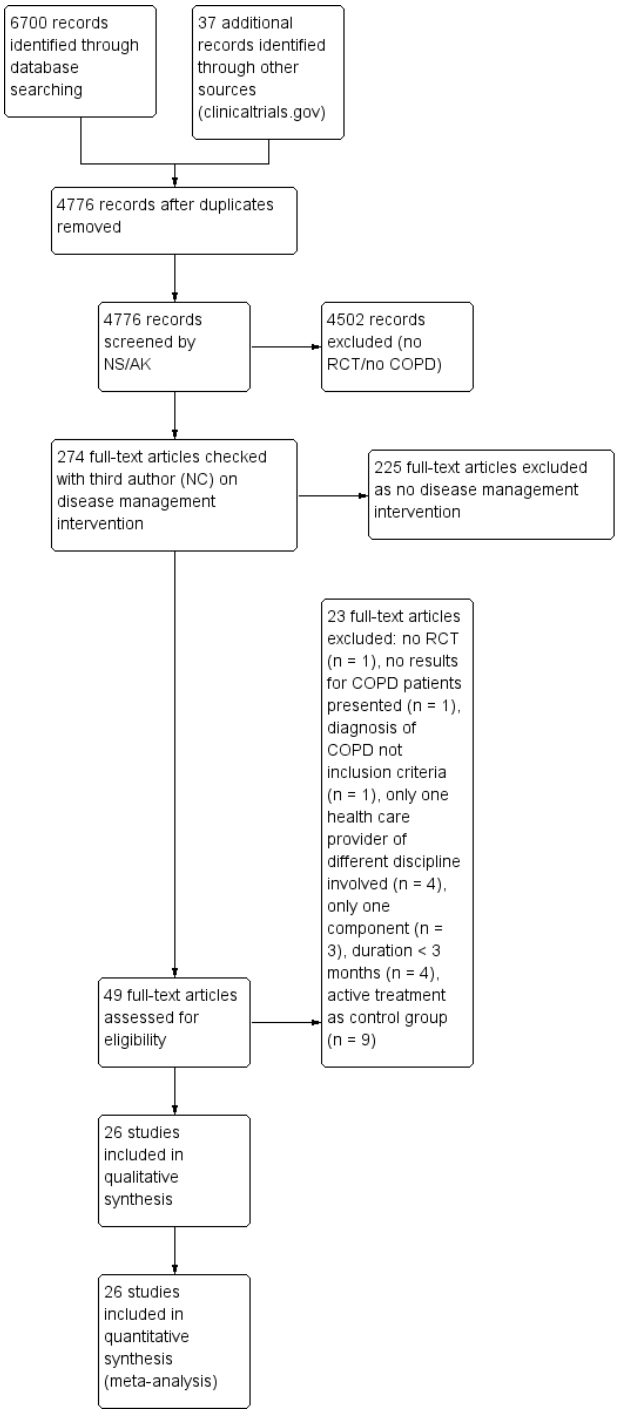
Description of studies

See Characteristics of included studies.

Results of the search

Our literature search identified 6700 titles and abstracts, resulting in 4776 references after de-duplication. Two review authors (AK, NS) screened the title/abstracts of these studies based on the predetermined inclusion criteria. Studies that were excluded because of the IDM intervention were double-checked by a third review author (NC). We retrieved the full-text articles of these studies and they were discussed in a consensus meeting. Finally, we identified 49 potentially relevant articles about IDM in COPD patients. We obtained full-text versions of these papers and data were extracted by one review author (AK) and double-checked by a second review author (NC). Finally, a total of 26 (cluster) randomised controlled trials were included in the review. The PRISMA flow diagram is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

Characteristics of the included studies are described in Table 1, Table 2 and Characteristics of included studies.

Twenty-six RCTs met the eligibility criteria for the review, of which two were cluster-randomized trials (Rea 2004; Wood-Baker 2006). One trial was a cross-over trial (Cambach 1997). The studies were published between 1994 and 2011. Five studies originated from the Netherlands (Wijkstra 1994; Strijbos 1996; Cambach 1997; van Wetering 2010; Trappenburg 2011), four studies from Spain (Güell 2000; Farrero 2001; Güell 2006; Fernandez 2009), three studies from Australia (Smith 1999; Boxall 2005; Wood-Baker 2006), three from the United Kingdom (Littlejohns 1991; Dheda 2004; Sridhar 2008) and three from the United States (Aiken 2006; Koff 2009; Rice 2010). Two studies were conducted in Denmark (Bendstrup 1997; Gottlieb 2011), two originated from Sweden (Engstrom 1999; Theander 2009) and one each from Brazil (Mendes 2010), Canada (Bourbeau 2003), Japan (Wakabayashi 2011) and New Zealand (Rea 2004).

Participants

A total of 2997 COPD patients were randomised in the 26 studies, with a range of 30 to 713 patients per study. Of these, 2523 (84%) patients completed the studies (range 18 to 725). The mean age of the study population was 68 years (SD 3.7), with 68% being male. Patients had a mean FEV1 % predicted of 44.3% (range 28 to 66).

Interventions

Patients were treated in all types of healthcare settings: primary care (eight studies), secondary care (12 studies), tertiary care (one study) and a combination of primary and secondary health care (five studies). The number of health care providers involved in the IDM program ranged from two to seven, with a mean number of three. Furthermore, we calculated the number of components per program, which ranged from two to eight, with a mean number of four.

A priori, we planned to arrange the interventions in order to perform subgroup analysis based on type of intervention, according to type of health care providers, different components, and frequency and duration of intervention. However, it was not possible to determine the mean intensity, frequency or duration of all programs, due to lack of data. Furthermore, as the studies were too heterogeneous, it was not possible to arrange programs according to different combinations of components or combinations of health care providers. Therefore, we determined the dominant component of the IDM program in all studies. The main component of the intervention could directly be determined in nine studies (Littlejohns 1991; Smith 1999; Farrero 2001; Bourbeau 2003; Dheda 2004; Aiken 2006; Wood-Baker 2006; Koff 2009; Trappenburg 2011) from the objective or title of the study. For example, in Aiken 2006: "*The objective is to document outcomes of a randomised trial of the PhoenixCare demonstration program of palliative care and coordinated care/case management for seriously chronically ill individuals who simultaneously received active treatment from managed care organizations. Intensive home-based case management provided by registered nurse case managers, in coordination with patients' existing source of medical care, comprised the intervention*".

In the remaining 17 studies, the main component was not directly clear from the objective. In 15 studies (Wijkstra 1994; Strijbos 1996; Bendstrup 1997; Cambach 1997; Engstrom 1999; Güell 2000; Boxall 2005; Güell 2006; Fernandez 2009; Theander 2009; Mendes 2010; Rice 2010; van Wetering 2010; Gottlieb 2011; Wakabayashi 2011), we chose the main component of the intervention as the component on which most of the time of the intervention was spent. For example: Bendstrup 1997: "*The intervention programme lasted 12 weeks. The programme consisted of the following components. Exercise training: the patients trained together at the hospital for 1h, three times a week for 12 weeks. Occupational therapy: two lessons each group. Education: 12 sessions. Smoking cessation: only for patients wishing to stop smoking.*"

In one study (Sridhar 2008) there were two components on which most of the time of the intervention was spent (exercise and self management action plan). In another study (Rea 2004) there were two main components: self management action plan and structured follow-up. Therefore we arranged these two studies as separate categories.

We made the following categories:

1. IDM dominant component exercise (13 studies: Wijkstra 1994; Strijbos 1996; Bendstrup 1997; Cambach 1997; Engstrom 1999; Güell 2000; Boxall 2005; Güell 2006; Fernandez 2009; Theander 2009; Mendes 2010; van Wetering 2010; Gottlieb 2011).
2. IDM dominant component self management with an exacerbation action plan (five studies: Bourbeau 2003; Wood-Baker 2006; Koff 2009; Rice 2010; Trappenburg 2011).
3. IDM structured follow-up with nurses/GP (five studies: Littlejohns 1991; Smith 1999; Farrero 2001; Dheda 2004; Aiken 2006).
4. IDM exercise and self management action plan (one study: Sridhar 2008).
5. IDM self management action plan and structured follow-up (one study: Rea 2004)
6. IDM program of educational sessions, follow by a phase of individually tailored education according to scores on the Lung Information Needs Questionnaire score (one study: Wakabayashi 2011).

In two studies, IDM was compared to another IDM intervention and a control group (Strijbos 1996; Mendes 2010). Both studies involved two intervention groups including an IDM program with a focus on exercise training and one control group. In both studies, we combined and pooled data from the two intervention arms as one group. One study had a cross-over design with drug treatment after three months (Cambach 1997). Therefore, we used solely the data for the intervention and control group at baseline and at three months.

Control groups consisted of usual care in 20 studies, in two studies control patients received a mono-disciplinary treatment including optimization of drug treatment (Cambach 1997; Güell 2006) and in four studies control patients received a treatment solely with education (Wood-Baker 2006; Fernandez 2009; Rice 2010; Wakabayashi 2011). Usual care consisted in all studies of regular follow-up visits to health care providers, which depended on the type of setting. There was access to health care providers on a 'need to' basis, without additional treatment or management programs. In all studies, no attempts were made to influence this usual care.

Outcomes

We recorded the number of studies reporting a specific outcome as follows:

- Quality of life (22 studies)
- Exercise capacity (18 studies)
- Exacerbation-related outcomes: measured by number of exacerbations; hospital admissions; hospitalisation days; emergency department (ED) visits; number of prednisolone or antibiotics courses (15 studies)
- Lung function (14 studies)
- Survival, mortality (five studies)
- Depression (four studies)
- Dyspnea, measured by MRC Dyspnea score (three studies) or Borg score (three studies)
- Co-ordination of care (three studies)

Details of the included studies are provided in Characteristics of included studies.

We requested additional data from the authors of 14 studies. Of these, 11 authors responded (79%) and six (43%) could provide us with additional data. Therefore, it was not necessary to impute missing data as described in our research protocol (see Dealing with missing data).

Excluded studies

After the first selection based on abstract and title, 49 potentially eligible studies were identified. Finally, after reading the full-text papers, we excluded 23 studies for one of the following reasons:

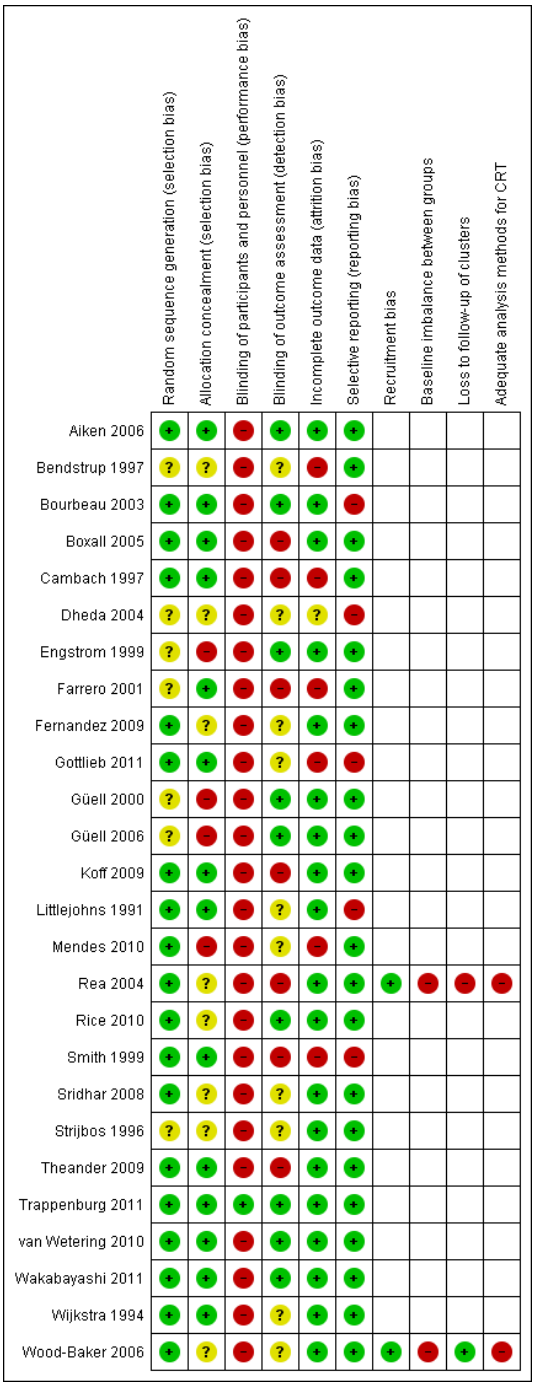
1. not a RCT (n = 1);
2. no diagnosis of COPD or no obtainable results reported for COPD as a subgroup (n = 2);
3. intervention includes one component of care (n = 3);
4. intervention includes one health care provider of different disciplines (n = 4);
5. duration of intervention is less than three months (n = 4);
6. active treatment as a control group (n = 9).

The reasons for exclusion are further specified in Characteristics of excluded studies. For ongoing studies, refer to Characteristics of ongoing studies.

Risk of bias in included studies

For full details of 'Risk of bias' judgments see Characteristics of included studies and for an overview see Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgments about each risk of bias item for each included study.



Allocation

Nineteen studies reported full details of adequate sequence generation and we judged them to be of low risk of bias. We judged the remaining seven studies as having unclear risk of bias as they were reported as randomised, but gave no description of the methods used to conceal the sequence. Fourteen studies reported adequate allocation concealment, while we judged four studies as high risk of bias. There were insufficient details for the remaining six studies for us to reach a firm conclusion so we judged them to be at unclear risk of bias. There were 13 studies in which both the sequence generation and concealment of allocation were adequately described, thus selection bias was minimized in these studies.

Blinding

The nature of the intervention precludes the possibility of blinding patients or health care providers. Therefore, we judged all the studies, except Trappenburg 2011, to be at high risk of performance bias. Trappenburg 2011 made a good attempt in using a modified informed consent procedure (postponed information), which meant that patients were unaware of the major aim of the study (education and an action plan), thereby enabling a single-blind study design (Trappenburg 2011). Therefore, we scored this study as low risk of bias. While blinding of health care providers and patients is impossible with this type of intervention, outcome assessors could be blinded to participants' allocation. This was reported in nine trials indicating a low risk of bias. Outcome assessors were unblinded in seven studies (high risk) and 10 studies provided insufficient information (unclear risk).

Incomplete outcome data

We judged 19 out of the 26 studies as low risk of bias, as they had low drop-out rates, drop-out rates were balanced across groups or trial authors performed an intention-to-treat analysis. We rated seven studies as high risk of bias and they were likely to be subject to attrition bias. Three out of these seven studies (Dheda 2004; Mendes 2010; Gottlieb 2011) had unbalanced drop-out rates, with higher rates in the intervention group compared to the control group. One study had a high drop-out rate balanced in both groups (31%) and the authors performed no intention-to treat-analysis (Bendstrup 1997). Cambach 1997 excluded all patients who did not return for one or more of the assessments from the final analyses. In Farrero 2001, quality of life was only investigated in the first 40 consecutive patients, therefore inducing risk of bias. In Smith 1999, all control participants refused to fill in the quality of life questionnaire and expressed that the burden of participating in a study, including questionnaires, was greater than expected.

Selective reporting

We rated 21 studies as low risk of bias and five studies as high risk of bias. Three studies (Rice 2010; van Wetering 2010; Trappenburg 2011) published a study protocol, with which we could compare the results sections. In the other studies, we checked whether the outcomes reported in the methods section of the article were reported in the results section. Five studies (Littlejohns 1991; Smith 1999; Bourbeau 2003; Dheda 2004; Gottlieb 2011) selectively reported outcomes. In two studies (Bourbeau 2003; Dheda 2004) the authors reported no statistically significant difference in the outcome and therefore did not present data, indicating selection bias. In the other three studies (Littlejohns 1991; Smith 1999; Gottlieb 2011), it remained unclear why it was planned to measure an outcome but it was not ultimately published.

Other potential sources of bias

We included two cluster-randomized trials (Rea 2004; Wood-Baker 2006). Unfortunately, both studies introduced noteworthy biases related to cluster-randomization in different ways. In one study (Wood-Baker 2006) recruitment bias remained unclear, as the authors provided insufficient information regarding the cluster-randomization process. In contrast, we judged Rea 2004 to have low risk of bias, as clusters were randomised before patients were recruited. Furthermore, we rated both studies as high risk of bias for baseline imbalance between groups, which could have been reduced when stratified or if pair-matched randomisation of the clusters had been used instead (Higgins 2011). In the Rea 2004 study, there was loss to follow-up of five clusters (four control and one intervention cluster), therefore this study was subject to bias. There was no follow-up of clusters in Wood-Baker 2006 (low risk of bias). Finally, both studies introduced bias as they analyzed data by incorrect statistical methods, not taking the clustering into account. This may account for the over-precise results and can result in much more weight in a meta-analysis (Higgins 2011). Therefore, in our meta-analyses we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). Based on similar primary care cluster-randomized trials, we used an intra-class correlation coefficient (ICC) of 0.01 (Kerry 1998; Campbell 2001). For dichotomous data, we divided both the number of participants and the number experiencing the event by the design effect. For continuous data, we reduced the sample sizes; means and standard deviations remained unchanged (Higgins 2011).

Effects of interventions

See: **Summary of findings for the main comparison** Integrated disease management compared to control for patients with chronic obstructive pulmonary disease

In the majority of the outcomes, heterogeneity was not encountered. However, there was substantial heterogeneity present in SGRQ total score, six-minute walk distance (6MWD), CRQ dyspnoea (long-term), hospital admissions for all causes, hospital days and ED visits. If possible, we performed sensitivity and subgroup analysis on these outcomes to see if the heterogeneity could be explained. Our a priori determined subgroup analysis based on type of health care provider and the frequency and duration of intervention was impossible, as there was large heterogeneity among combinations of health care providers and the exact composition in terms of duration, frequency and intensity of programs was often not clearly reported. In addition, we were not able to perform subgroup analysis on GOLD stage or MRC Dyspnea score, as most studies did not report GOLD stages or MRC Dyspnea score. Furthermore, the definitions and classifications of GOLD stages have been changed over the years, resulting in large variation in severity within subgroups.

Instead, we performed subgroup analysis based on type of setting of the intervention (primary, secondary, tertiary care) and type of control group. Furthermore, we performed subgroup analysis with regard to the dominant component of the IDM program.

We used unadjusted data for meta-analyses, as only unadjusted data were reported, with the exception of two studies (van Wetering 2010; Trappenburg 2011).

Primary outcomes

1. Quality of life

Of the 26 included studies, 23 measured HRQoL using six different instruments (see Characteristics of included studies):

1. St. George's Respiratory Questionnaire (SGRQ) (13 studies);
2. Chronic Respiratory Questionnaire (CRQ) (eight studies);
3. Short Form-36 (SF-36) (three studies);
4. Sickness Impact Profile (SIP) (two studies);
5. Dartmouth Primary Care Co-operative Quality of Life questionnaire (COOP) (one study).

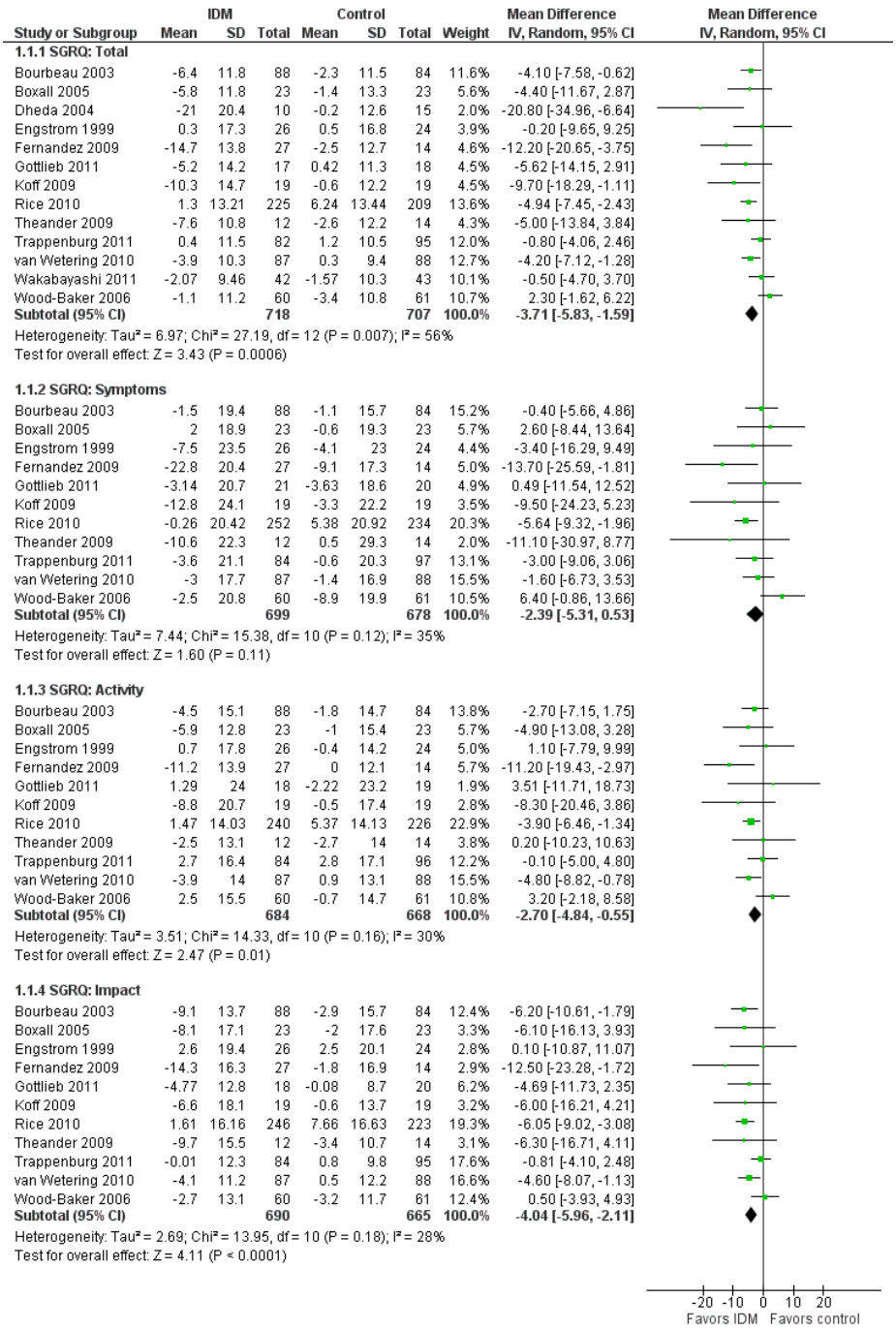
The SGRQ and CRQ are both disease-specific quality of life questionnaires. However, a meta-analysis combining CRQ and SGRQ score should not be used as Puhan 2006 has shown that the CRQ is more responsive than the SGRQ. Furthermore, the included generic quality of life questionnaires (SF-36, SIP and COOP) measure other dimensions of generic health quality of life, and therefore combining data in a meta-analysis across tools was not possible.

1.1 Respiratory-specific QoL

1.1.1.1 SGRQ total score - short-term

The SGRQ is a disease-specific, validated questionnaire with a scale from 0 (good health) to 100 (worse health status). A negative sign on this questionnaire indicates improvement, and the minimal clinically important difference (MCID) is -4 points (Jones 1991). Thirteen studies with a total population of 1425 patients provided data on the SGRQ total score with a follow-up of 3 to 12 months (Engstrom 1999; Bourbeau 2003; Dheda 2004; Boxall 2005; Wood-Baker 2006; Koff 2009; Fernandez 2009; Theander 2009; Rice 2010; van Wetering 2010; Gottlieb 2011; Trappenburg 2011; Wakabayashi 2011). The pooled mean difference (MD) on the SGRQ total score was -3.71 in favor of IDM (95% confidence interval (CI) of -5.83 to -1.59; Analysis 1.1; Figure 3; Summary of findings for the main comparison) which reached statistical significance ($P < 0.001$) and was close to, but did not reach, the MCID of -4 points. In other words, those treated with IDM had 3.71 out of 100 points better quality of life on this questionnaire. Pooling indicated a high degree of heterogeneity ($I^2 = 56\%$, $P = 0.01$). Heterogeneity was due to differences in the quality of studies. We were able to reduce heterogeneity if we performed multiple sensitivity analyses based on studies with adequate allocation concealment, adequate blinding of outcome assessment, cluster-randomization bias, or studies analyzing outcomes by intention-to-treat. Sensitivity analysis on studies with adequate allocation concealment (Bourbeau 2003; Boxall 2005; Koff 2009; Theander 2009; van Wetering 2010; Gottlieb 2011; Trappenburg 2011; Wakabayashi 2011) demonstrated that there was still a statistically significant effect in favor of the intervention group (MD -3.16; 95% CI -4.75 to -1.57, $P < 0.001$). In the same way, in trials (Engstrom 1999; Bourbeau 2003; van Wetering 2010; Rice 2010; Trappenburg 2011; Wakabayashi 2011) with adequate blinding of outcome assessment the effect did not change (MD -3.16; 95% CI -4.81 to -1.51, $P < 0.001$). A sensitivity analysis excluding the cluster-randomized study of Wood-Baker 2006, in which there was an unclear risk of recruitment bias and a high risk of bias on baseline imbalance, the effect changed to a clinically and statistically significant MD in favor of IDM (-4.22; 95% CI -6.14 to -2.30, $P < 0.001$). Lastly, a sensitivity analysis on the studies that analyzed the data using the intention-to-treat principle (Bourbeau 2003; Rice 2010) showed a statistically significant and clinically relevant difference in favor of IDM (MD -4.65; 95% CI -6.69 to -2.62, $P < 0.0001$) compared to controls.

Figure 3. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.1 SGRQ: short-term (3 to 12 months).



Subgroup analysis based on type of setting

There were six studies conducted in primary care on 456 participants (Boxall 2005; Wood-Baker 2006; Koff 2009; Fernandez 2009; van Wetering 2010; Gottlieb 2011) and seven studies in secondary care on 969 participants (Engstrom 1999; Bourbeau 2003; Dheda 2004; Theander 2009; Rice 2010; Trappenburg 2011; Wakabayashi 2011). No studies were performed in tertiary care. Subgroup analysis based on primary care studies showed a clinically relevant mean difference of -4.68 (95% CI -8.80 to -0.56) in favor of IDM. This result was statistically significant and clinically relevant. Subgroup analysis on secondary care studies showed a statistically significant difference of -3.41 (95% CI -5.97 to -0.85)(Analysis 1.3). This difference was not clinically relevant. The test for subgroup difference did not show a statistically significant difference in treatment effects in patients treated in different types of health care setting (Chi^2 = 0.27, df = 1 (P = 0.61)).

Subgroup analysis based on study design

We performed subgroup analysis based on study design and compared RCTs (n = 1304) versus cluster-RCTs (n = 121). There was no difference in SGRQ total score between intervention and control in the cluster-RCT of Wood-Baker 2006 (MD 2.30; 95% CI -1.62 to 6.22; Analysis 1.4). Pooled meta-analysis of RCTs showed a clinically relevant effect in favor of the IDM group of -4.22 (95% CI -6.14 to -2.30, P < 0.0001). The test for subgroup differences showed a statistically significant difference between the pooled analysis of the RCTs and the effect in the cluster-RCT (Chi^2 = 8.57, df = 1 (P = 0.003)).

Subgroup analysis based on type of control group

In nine studies including 744 participants, control patients received usual care, and in four studies (n = 681) the control group received a mono-disciplinary treatment of education. Meta-analysis of the usual care studies showed a significant difference between groups of -4.09 (95% CI -6.35 to -1.84, P < 0.001) (Analysis 1.5). Subgroup analysis of studies in which the control group received education showed no significant difference in effect between groups (MD -2.98; 95% CI -7.69 to 1.74, P = 0.022), which was neither statistically nor clinically relevant. There was no statistically significant difference in the test for subgroup difference (Chi^2 = 0.17, df = 1 (P = 0.68)).

Subgroup analysis based on dominant component of the program

There were four studies including 942 patients (Bourbeau 2003; Wood-Baker 2006; Koff 2009; Rice 2010) in which self management was the dominant component, and six studies including 373 patients in which exercise training was the dominant component (Engstrom 1999; Boxall 2005; Theander 2009; Fernandez 2009; van Wetering 2010; Gottlieb 2011). One study (Wakabayashi 2011) evaluated an individual tailored education program and one study (Dheda 2004) focused mainly on structured follow-up with nurses and GPs. Subgroup analysis of the self management studies revealed neither a statistically nor a clinically relevant mean difference: MD -2.76 (95% CI -5.88 to 0.36, P = 0.08). Subgroup analysis of exercise studies showed a statistically and clinically relevant difference of -4.74 in favor of IDM (95% CI -7.05 to -2.43, P < 0.0001). There was no statistically significant difference between subgroups (Chi^2 = 1.00, df = 1 (P = 0.32)) (Analysis 1.6).

1.1.1.2. SGRQ - long-term

Two studies including 189 participants measured the long-term effect on the SGRQ total score: at 18 (Gottlieb 2011) and 24 (van Wetering 2010) months follow-up. There was no statistically significant difference between groups (MD -0.22; 95% CI -7.43 to 6.99, P = 0.95; I^2 = 54%, P = 0.14)(Analysis 1.2).

1.1.2.1 SGRQ domain scores - short-term

Eleven studies with a total population of 1377 patients reported scores on the SGRQ domains of symptoms, activity and impact. For all domains, there was no significant heterogeneity (I^2 between 35% and 28%) (Analysis 1.1). We found the following results:

- Symptom domain: MD -2.39 (95% CI -5.31 to 0.53, P = 0.11)
- Activity domain: MD -2.70 (95% CI -4.84 to -0.55, P = 0.01)
- Impact domain: MD -4.04 (95% CI -5.96 to -2.11, P < 0.0001)

1.1.2.2. SGRQ domain scores - long-term

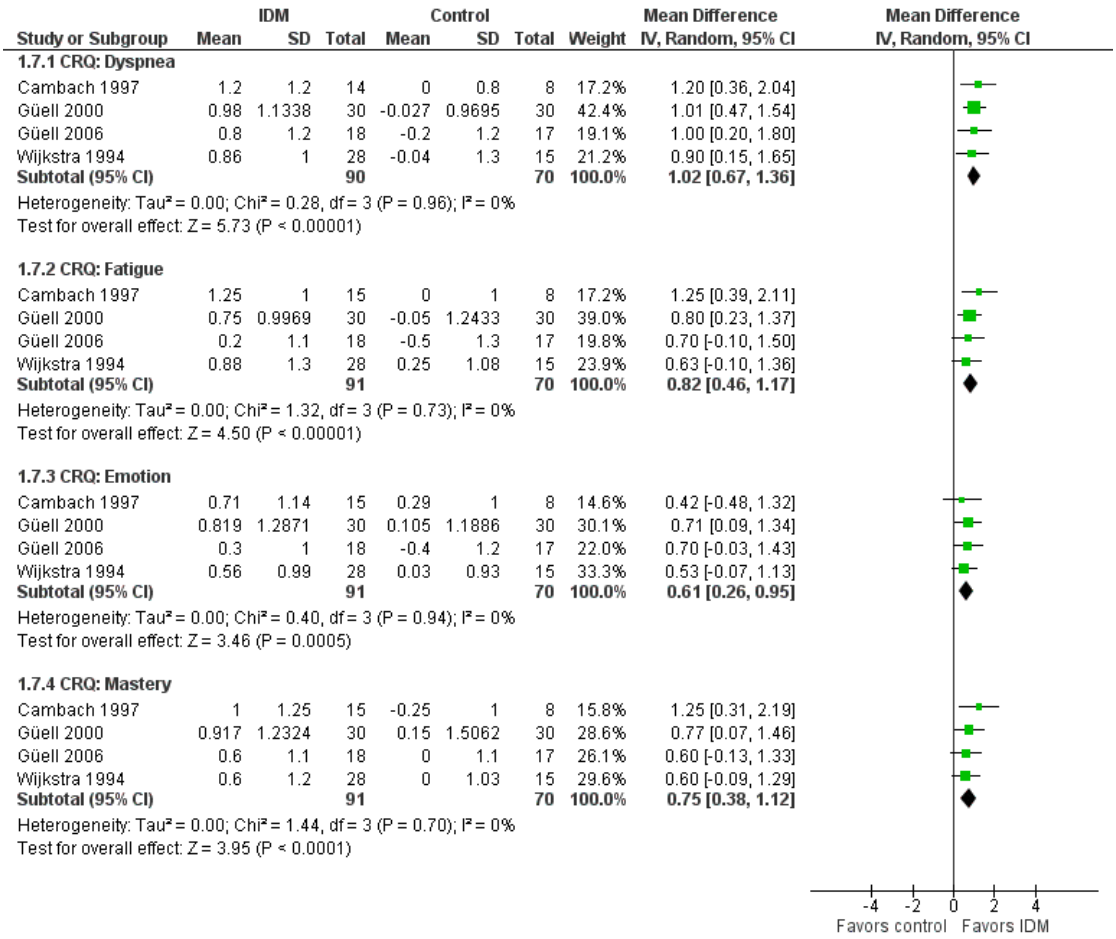
Two studies measured the long-term effect on the SGRQ at 18 months (van Wetering 2010; Gottlieb 2011). Mean differences on all domains had wide confidence intervals and included zero (Analysis 1.2).

1.1.3.1. CRQ domain scores - short-term

The Chronic Respiratory Disease Questionnaire (CRQ), with a scale from 0 to 7 and a MCID of 0.5, was reported in eight trials (Wijkstra 1994; Bendstrup 1997; Cambach 1997; Güell 2000;

Farrero 2001; Rea 2004; Güell 2006; Sridhar 2008). Three of these (Bendstrup 1997; Farrero 2001; Rea 2004) could not be used in a meta-analysis. Bendstrup 1997 and Rea 2004 reported insufficient data and the authors could not provide us with additional data. In addition, Farrero 2001 administered the CRQ in the first 40 consecutive patients and therefore outcomes were not published. The pooled results of four studies including 160 participants (Wijkstra 1994; Cambach 1997; Güell 2000; Güell 2006) measuring the CRQ until 12 months follow-up are shown in Figure 4 and Analysis 1.7. For each of the CRQ domains, the MD was well above the MCID of 0.5 units and differences in scores were statistically significant: dyspnoea (MD 1.02; 95% CI 0.67 to 1.36, P < 0.0001), fatigue (MD 0.82; 95% CI 0.46 to 1.17, P < 0.0001), emotion (MD 0.61; 95% CI 0.26 to 0.95, P < 0.0005) and mastery (MD 0.75; 95% CI 0.38 to 1.12, P < 0.0001). The results showed homogeneity across studies.

Figure 4. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.7 CRQ: short-term (3 to 12 months).



1.1.3.2. CRQ domain scores - long-term

Two studies (n = 151) (Güell 2000; Sridhar 2008) measured the long-term effectiveness on CRQ domain scores at 24 months follow-up(Analysis 1.8). There was no difference between groups on the CRQ dyspnoea domain: MD 0.47 (95% CI -0.31 to 1.25, P = 0.24). Pooled data showed substantial heterogeneity (I^2 = 70%, P = 0.07), which was related to differences in the type of interven-

tion (exercise in the Güell 2000 study versus structured follow-up with a respiratory nurse and exacerbation plan in Sridhar 2008). Güell 2000 demonstrated a significant difference in favor of IDM (MD 0.92; 95% CI 0.19 to 1.65, P = 0.01). In contrast, there was no statistically significant difference between groups on the CRQ dyspnoea domain in Sridhar 2008 (MD 0.12; 95% CI -0.32 to 0.58, P = 0.61).

Pooled mean differences on the domains fatigue, emotion and mastery showed homogeneity across studies. On the CRQ fatigue domain, there was a statistically significant but not clinically relevant difference of 0.45 in favor of IDM (95% CI 0.05 to 0.85, P = 0.03). On the CRQ emotion and mastery domain, the statistically and clinically relevant effect was in favor of IDM: emotion MD 0.53 (95% CI 0.10 to 0.95, P = 0.02) and mastery MD 0.80 (95% CI 0.37 to 1.23, P < 0.01).

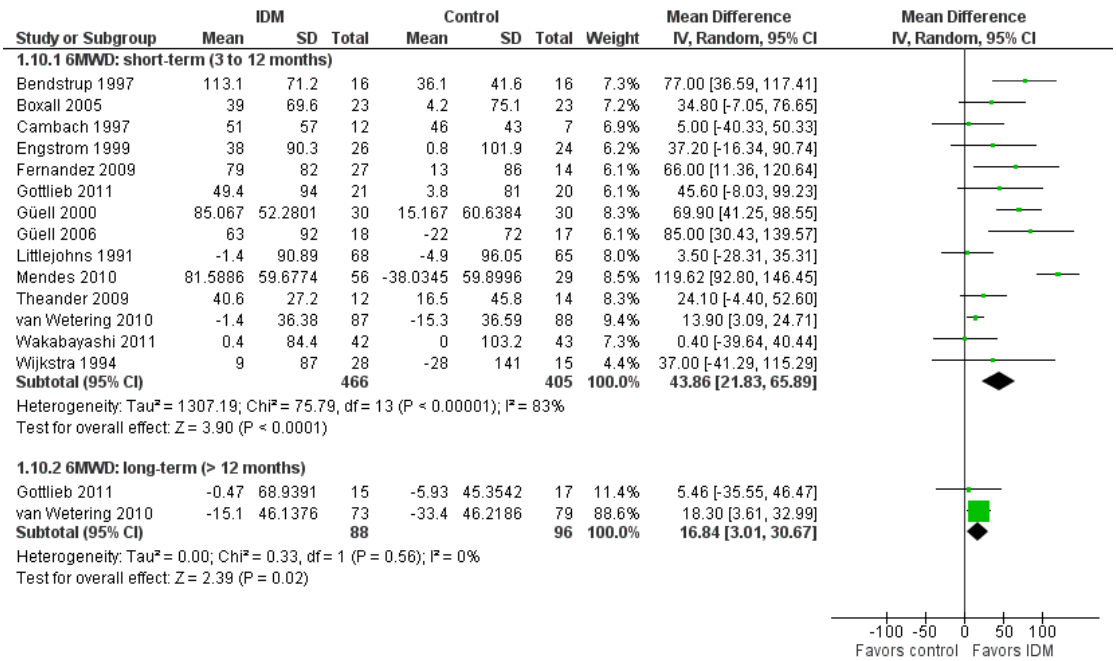
1.2 General health-related QoL

General HRQoL was measured with the SF-36 in three studies (Dheda 2004; Rea 2004; Aiken 2006). The authors of these studies could not provide us with sufficient data for pooling in a meta-analysis. Neither study found a significant effect between groups. Two of these studies (Dheda 2004; Aiken 2006) suffer from small sample sizes varying from 15 to 10 patients per group per study, which makes it difficult to detect an effect (underpowered studies). We pooled the data from two studies (Littlejohns 1991; Engstrom 1999) reporting data on the SIP (Analysis 1.9). No between-group differences in any domain of the SIP were found. One other study used the York Quality of Life Questionnaire (Bendstrup 1997) and reported no significant difference. Smith 1999 used a modified version of the Dartmouth Primary COOP. In this study, the authors analyzed only the data from the intervention group (n = 30) due to lack of data in the control group. The authors concluded that the total COOP scores in the intervention group significantly improved HRQoL at 12 months.

2. Exercise capacity

Seventeen studies measured exercise capacity using either the 6MWD or the cycle ergometer test. The MCID on the 6MWD is estimated at 35 meters (Puhan 2008). There is no MCID reported in the current literature for the cycle ergometer test. Results are shown in Figure 5.

Figure 5. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.10 Functional exercise capacity: 6MWD mean difference.



2.1.1 Functional exercise capacity - short-term

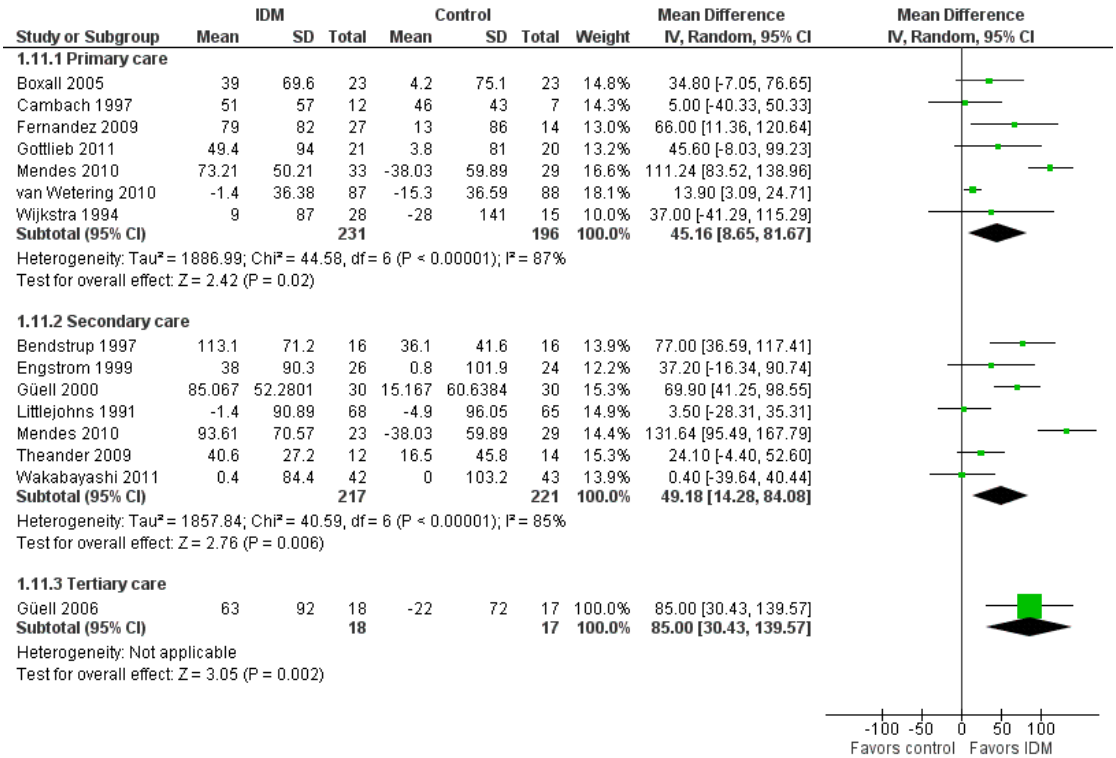
We pooled data from 14 studies using the 6MWD including 871 participants. One study could not be pooled, as the authors reported no data because there was no significant difference between groups at 12 months follow-up (Bourbeau 2003).

Patients treated with IDM improved their 6MWD by a statistically and clinically relevant 43.86 meters (95% CI 21.83 to 65.89)(Figure 5; Analysis 1.10). There was heterogeneity between the results of the studies (I^2 = 83%). This heterogeneity is explained by differences in the quality of studies. We performed sensitivity analysis on studies with adequate allocation concealment, which reduced heterogeneity (I^2 = 0%) and reduced the effect to a MD of 15.15 meters, which was still statistically significant (95% CI 6.37 to 23.93, P < 0.001), however no longer clinically relevant. Furthermore, we performed subgroup analysis based on type of setting, type of control group and dominant component of the intervention.

Subgroup analysis based on type of setting

There were seven studies with 427 participants (Wijkstra 1994; Cambach 1997; Boxall 2005; Fernandez 2009; van Wetering 2010; Mendes 2010; Gottlieb 2011) conducted in primary care, seven studies with 438 participants (Littlejohns 1991; Bendstrup 1997; Engstrom 1999; Güell 2000; Theander 2009; Mendes 2010; Wakabayashi 2011) in secondary care and one study in tertiary care with 35 participants (Güell 2006). Both subgroup analyses showed similar statistically and clinically relevant improvements: exercise training in primary care revealed a MD of 45.16 meters (95% CI 8.65 to 81.67, P = 0.02), whereas in the secondary care setting the MD was 49.18 meters (95% CI 14.28 to 84.08, P = 0.006). The tertiary care study showed a significant effect in favor of IDM of 85 meters (95% CI 30.43 to 139.57). Results are shown in Analysis 1.11 and Figure 6.

Figure 6. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.11 Subgroup analysis 6MWD based on type of setting.



Subgroup analysis based on control group

We pooled four studies with 180 participants in which control patients received a treatment with optimal medication (Cambach 1997; Güell 2006) or an education session (Fernandez 2009; Wakabayashi 2011) in a subgroup analysis. In the same way, we pooled 10 studies (Littlejohns 1991; Wijkstra 1994; Bendstrup 1997; Engstrom 1999; Güell 2000; Boxall 2005; Theander 2009; Mendes 2010; van Wetering 2010; Gottlieb 2011) including 691 participants in which the control group consisted of usual care. Subgroup analysis in which one component of treatment was used showed no difference between groups (MD 35.99; 95% CI -5.34 to 77.31, P = 0.09)(Analysis 1.12). In studies in which the control group consisted of usual care, the 6MWD improved clinically and statistically significantly by 46.59 meters in favor of IDM (95% CI 19.68 to 73.51, P = 0.0007). However, the test for subgroup differences did not show any difference between control groups (Chi^2 = 0.18, df = 1 (P = 0.67)).

Subgroup analysis based on dominant component of intervention

Twelve out of the 14 studies (n = 653) measuring exercise capacity incorporated some kind of exercise training in their IDM programs. We performed subgroup analysis, which showed that the 6MWD improved by 51.47 meters (95% CI 26.53 to 76.40). This effect was statistically and clinically relevant. In the remaining two studies (n = 218), exercise was not part of the IDM programs. In one study (Wakabayashi 2011), which consisted of individually tailored education sessions, there was no difference between groups (MD 0.40; 95% CI -39.64 to 40.44, P = 0.98). The other study (Littlejohns 1991), in which there was a focus on structured follow-up with GP and nurses, revealed no effect (MD 3.50; 95% CI -28.31 to 35.31, P = 0.83). In conclusion, studies incorporating exercise training in their IDM programs demonstrated larger effect sizes; this was statistically significant using the test for subgroup difference (Chi^2 = 7.49, df = 2 (P = 0.02))(Analysis 1.13).

2.1.2 Functional exercise capacity - long-term

Two studies on 184 participants published long-term results on the 6MWD (van Wetering 2010; Gottlieb 2011). Both studies showed that IDM statistically significantly improved exercise capacity measured on the 6MWD by 16.8 meters (MD 16.84; 95% CI 3.01 to 30.67) compared to the control group. However, this effect did not exceed the MCID. There was no heterogeneity present. Results are shown in Figure 5 and Analysis 1.10.

2.2. Maximal exercise capacity

Four studies on 298 participants assessed the maximal exercise capacity (in Watts) using the cycle ergometer test. Both studies showed that IDM statistically significantly improved the maximal exercise capacity by 7 Watts (MD 6.99; 95% CI 2.96 to 11.02, P < 0.0001)(Analysis 1.14).

3. Exacerbations

3.1.1 Number of patients experiencing at least one exacerbation - short-term

Two studies (Bourbeau 2003; Trappenburg 2011) including 407 patients reported on the number of patients experiencing at least one exacerbation during 12 months of follow-up. Both studies used the same definition and defined an exacerbation as an increase in symptoms, with deterioration of dyspnoea or purulent sputum. Pooled meta-analysis showed homogeneity and a pooled OR of 1.21 (95% CI 0.77 to 1.91) (Analysis 1.15), which showed no statistically or clinically relevant difference between groups. The trial authors of the Bourbeau 2003 study reported that although there were more patients experiencing at least one exacerbation in the intervention group (85 versus 81), the total number of exacerbations was higher in the control group (362) compared to the intervention group (299). This was of borderline significance (P = 0.06). Similarly, the number of patients experiencing three or more exacerbations during 12-month follow-up was higher in the control group (67.9%), compared to the action plan group (62.3%). Exacerbations in the intervention group were treated successfully at an early stage, which probably resulted in fewer patients with a hospital admission (17.2% versus 36.3%, P < 0.01). Trappenburg 2011 reported similar findings: although exacerbation rates did not differ between groups, exacerbations in the action plan group were perceived as substantially milder by patients, and they reported on average three days faster than those in the control group.

3.1.2. Number of patients experiencing at least one exacerbation - long-term

Two studies (Sridhar 2008; van Wetering 2010) including 301 patients assessed the number of patients experiencing at least one exacerbation at 24 months follow-up. Both studies related the definition of an exacerbation to health care. Sridhar 2008 stated they defined an exacerbation as the "*unscheduled need for healthcare, or need for steroid tablets, or antibiotics for worsening of their COPD*". Similarly, van Wetering 2010 defined a moderate exacerbation as "*a visit to the general practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient, was related to a COPD exacerbation. A severe exacerbation was defined as a hospitalisation for a COPD exacerbation*". Pooled meta-analysis demonstrated no difference between groups (OR 1.53; 95% CI 0.90 to 2.60, P = 0.12) (Analysis 1.16). There was homogeneity between studies. Sridhar 2008 stated that patients in the intervention group were more likely to have exacerbations treated with oral steroids alone or oral steroids and antibiotics than the control group. The initiator of treatment was statistically more likely to be the patient themselves compared to the GP in the control group.

3.1.3 Mean exacerbation rate - long-term

Two studies (Güell 2000; van Wetering 2010) including 226 participants reported on the exacerbation rate in both groups at 24 months follow-up. Data on exacerbations were skewed in the van Wetering study, therefore we decided not to pool both studies in a meta-analysis. In Güell 2006, control group patients (n = 23) experienced 207 exacerbations, with an average of 6.9 (3.9) exacerbations per patients, ranging from 0 to 16 exacerbations during the 24 months. The IDM group experienced 111 exacerbations, with an average of 3.7 (2.2) exacerbations per patients, ranging from 0 to 9 exacerbations during the 24 months. This difference was statistically significant (P < 0.0001) favoring IDM. In van Wetering 2010, the exacerbation rate was 2.78 in the IDM group and 2.16 in the control group, resulting in a rate ratio of 1.29 (95% CI 0.89 to 1.87), which was not statistically significant (P = 0.113).

3.2.1 Hospital admissions, all causes - short-term

Two studies on 266 participants (Littlejohns 1991; Rea 2004) reported data on the number of patients who were admitted for all causes until 12 months follow-up. There was no heterogeneity and there was no difference between groups (OR 0.62; 95% CI 0.36 to 1.07, P = 0.49) (Analysis 1.17).

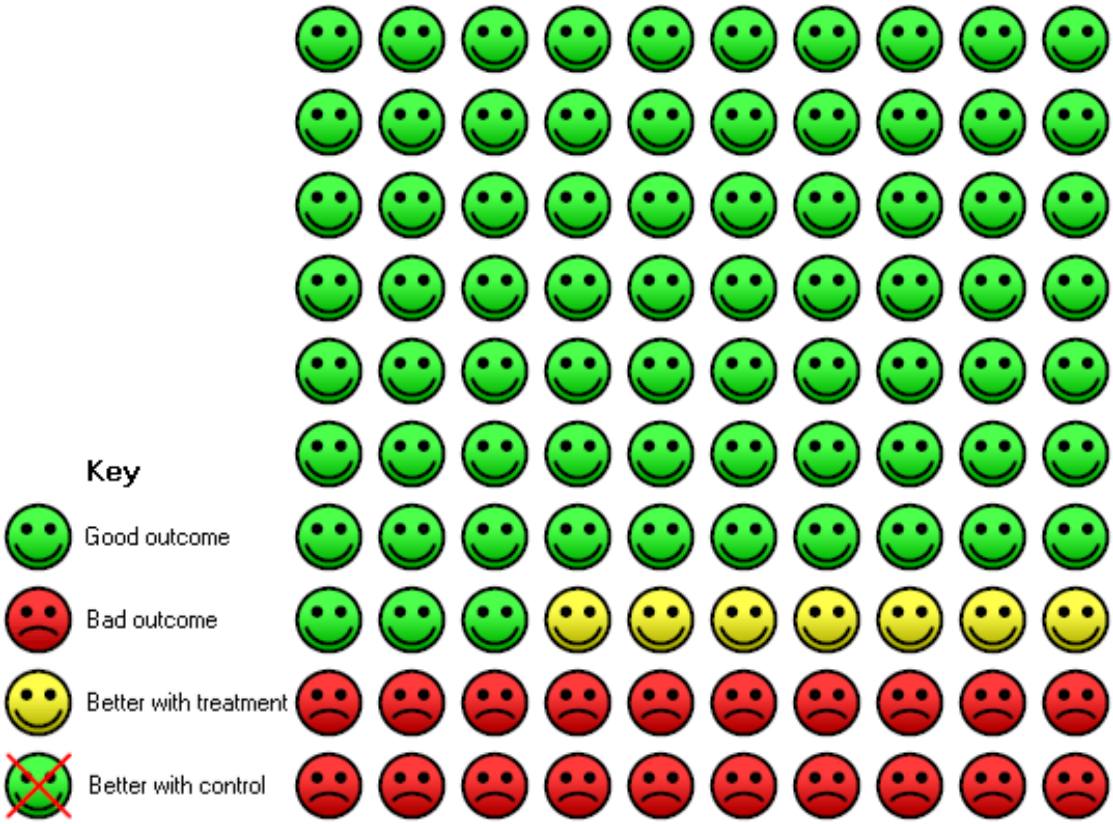
3.2.2. Hospital admissions, all causes - long-term

Two studies including a total of 283 patients (Sridhar 2008; van Wetering 2010) assessed the number of patients admitted until 24 months follow-up. Pooled results showed heterogeneity (I^2 = 53%), which could be explained as van Wetering 2010 showed a positive effect in favor of IDM and Sridhar 2008 showed no significant difference in effect between groups. Therefore, a pooled meta-analysis showed no difference between groups (OR 0.78; 95% CI 0.38 to 1.57)(Analysis 1.18).

3.3.1. Respiratory-related admissions - short-term

We pooled data from seven studies (Smith 1999; Bourbeau 2003; Rea 2004; Boxall 2005; Koff 2009; Rice 2010; Trappenburg 2011) measuring respiratory-related admissions until 12 months follow-up in a meta-analysis. Studies were homogeneous. Pooled estimates showed a statistically significant difference in favor of IDM (OR 0.68; 95% CI 0.47 to 0.99, P = 0.04)(Analysis 1.19). In the control group 27 people out of 100 had a respiratory-related hospital admission over 3 to 12 months, compared to 20 (95% CI 15 to 27) out of 100 in the integrated disease management group, as presented in Figure 7. Over the course of a year, the number needed to treat with IDM to prevent one hospital admission was NNT(B) 15 (95% CI 9 to 506).

Figure 7. In the control group 27 people out of 100 had a respiratory-related hospital admission over 3 to 12 months, compared to 20 (95% CI 15 to 27) out of 100 for integrated disease management group.



3.3.2. Respiratory-related admissions - long-term

Data from one trial (van Wetering 2010) presented data on the number of patients admitted until 24 months follow-up. There was no difference between the control and IDM group on the number of respiratory-related admissions (OR 0.59; 95% CI 0.28 to 1.22, P = 0.16)(Analysis 1.20).

3.4.1 Hospital days per patient - short-term

Six studies on 741 patients (Engstrom 1999; Farrero 2001; Bourbeau 2003; Rea 2004; Boxall 2005; Trappenburg 2011) reported the difference in mean hospitalisation days per patient per group (intervention versus control). Patients treated with IDM were on average discharged from the hospital nearly four days earlier compared to control patients, with a confidence interval from six to two days (MD -3.78; 95% CI -5.90 to -1.67, P < 0.001) (Analysis 1.21). There was heterogeneity in the results (I^2 = 55%). Inspection of the forest plot shows that this was the result of one outlying study (Engstrom 1999), which reported more days for intervention patients. The authors stated that the data on admission days in his study were skewed, as one patient accounted for 50% of the increase in the IDM group. Reanalysis with exclusion of this trial did not change the significance, direction or effect of the mean difference.

3.4.2. Hospital days per patient - long-term

One trial with 175 patients (van Wetering 2010) reported the difference in mean number of total hospital days per patient per group at 24 months follow-up. There was no difference between groups (MD 0.60; 95% CI -3.01 to 4.21, P = 0.74) (Analysis 1.22).

3.5 Emergency Department (ED) visits

Six trials (Smith 1999; Farrero 2001; Bourbeau 2003; Rea 2004; Rice 2010; Wakabayashi 2011) assessed in various ways the number of ED visits. We were able to pool the data from four studies with 1161 patients (Smith 1999; Bourbeau 2003; Rea 2004; Rice 2010), which revealed no difference between groups with high

heterogeneity (OR 0.64; 95% CI 0.33 to 1.25; I^2 = 71%)(Analysis 1.23). Sensitivity analysis on two studies which analyzed by intention-to-treat and which blinded outcome assessors revealed a mean difference of 0.49 in favor of the control group (MD 0.49; 95% CI 0.36 to 0.67, P < 0.0001, I^2 = 0%). Three studies could not be pooled, due to lack of required data. Of these excluded studies, Trappenburg 2011 and Wakabayashi 2011 reported the mean ED visits per patient at baseline and follow-up. Both studies concluded no statistically significant difference between groups compared to baseline. On the other hand, Farrero 2001 reported a significant decrease in ED visits per patient in favor of the IDM group (0.45 ± 0.83 for intervention group, 1.58 ± 1.96 for control group; P = 0.0001). There were no data presented on the number of ED visits at long-term follow-up.

3.6 Patients using at least one course of oral steroids

We pooled data from three studies including 348 patients (Littlejohns 1991; Farrero 2001; Rea 2004) on the number of patients using at least one course of oral steroids until 12 months follow-up. Results were homogeneous and there was no difference between groups (OR 1.13; 95% CI 0.64 to 2.01, P = 0.66) (Analysis 1.24).

3.7. Patients using at least one course of antibiotics

There were two studies with 236 participants (Littlejohns 1991; Rea 2004) reporting on the number of patients using at least one course of antibiotics. The studies presented conflicting results and heterogeneity was large, as Rea 2004 was a primary care, cluster-randomized trial and Littlejohns 1991 was a RCT in the secondary care setting. The number of patients using at least one course of antibiotics was not different between groups, and the OR had a wide confidence interval (OR 1.43; 95% CI 0.24 to 8.48, P = 0.69)(Analysis 1.25).

Secondary outcomes

4. Dyspnea

Four studies reported the MRC Dyspnea Scale as an outcome (Mendes 2010; van Wetering 2010; Gottlieb 2011; Wakabayashi 2011), however Gottlieb failed to publish any results. We pooled data from the remaining three studies, including 345 patients. Dyspnea was improved in the IDM group by -0.30 points (MD -0.30; 95% CI -0.48 to -0.11, I^2 = 0%, P < 0.001)(Analysis 1.26). Furthermore, three studies on 145 patients used the Borg score to detect changes in perceived dyspnoea (Güell 2000; Boxall 2005; Gottlieb 2011). These data were pooled and revealed no change in dyspnoea (MD 0.14; 95% CI -0.70 to 0.98, P = 0.74, I^2 = 39%)(Analysis 1.27).

5. Mortality

Five trials assessing 1207 patients explicitly recorded mortality as an outcome. Of these, four trials assessed mortality at 12 months (Littlejohns 1991; Smith 1999; Farrero 2001; Rice 2010) and one study at 24 months (Sridhar 2008). There was no statistically significant difference between groups at short- (OR 0.96; 95% CI 0.52 to 1.74, P = 0.33; I^2 = 59%) and long-term follow-up (OR 0.45; 95% CI 0.16 to 1.28, P = 0.13) (Analysis 1.28). Heterogeneity in the short-term studies is due to different dominant components of the interventions.

6. Lung function

Lung function was measured in three different ways in 10 trials (Littlejohns 1991; Wijkstra 1994; Güell 2000; Farrero 2001; Bourbeau 2003; Wood-Baker 2006; Sridhar 2008; Fernandez 2009; van Wetering 2010; Wakabayashi 2011). Therefore, we created three different subgroups, which we pooled in two different meta-analyses: forced expiratory volume in one second (FEV1) in liters and FEV1 as per cent predicted for age, gender and height (FEV1% predicted), as well as the mean difference in FEV1% predicted from baseline. All pooled data on short- as well as on long-term outcome revealed no significant difference in lung function between groups(Analysis 1.29; Analysis 1.30).

7. Anxiety and depression

Four studies assessed depression as an outcome (Engstrom 1999; Littlejohns 1991; Güell 2006; Trappenburg 2011). Two studies (Littlejohns 1991; Trappenburg 2011) used the HADS, one study (Engstrom 1999) used the Mood Adjective Check List (MACL) and one study (Güell 2006) used a Revised Symptom Checklist. We pooled results on the HADS in a meta-analysis including 316 patients, which revealed no statistically significant difference between groups for anxiety (MD 0.22; 95% CI -0.41 to 0.85, I^2 = 0%) or depression (MD 0.21, 95% CI -0.39 to 0.81, I^2 = 0%)(Analysis 1.31). Engstrom 1999 used the MACL, a shortened 38-item version covering three basic dimensions of mood: pleasantness/unpleasantness, activation/deactivation and calmness/tension. No significant differences were found between groups. The aim of Güell 2006 was specifically to evaluate the effect of a pulmonary rehabilitation program on psychosocial morbidity (without including any specific psychological intervention), as well as effort capacity and HRQoL. Therefore, the authors used a Revised Symptom Checklist, containing 90 items, which included depression and anxiety. Following a per protocol analysis, the intervention group showed a significant improvement in depression ($P \leq 0.01$) and anxiety ($P \leq 0.05$).

8. Co-ordination of care

Three studies (Littlejohns 1991; Bendstrup 1997; Koff 2009) reported in some way on the co-ordination of care. However, these

studies had different intervention programs and reported on coordination of care in different ways. Therefore, interpretation of outcomes is difficult. Bendstrup 1997 reported an attendance rate of 78% of patients following a 12-week IDM program (consisting of education, exercise training, smoking cessation and occupational therapy).

Patient satisfaction with regard to the provided health care was measured in two studies. In Koff 2009, satisfaction with a self management/action plan program was assessed on a scale from 1 to 10 in the intervention group, with 1 being strongly dissatisfied and 10 completely satisfied. Patients expressed high satisfaction with all of the equipment used, except for the pedometer. Littlejohns 1991 designed a satisfaction questionnaire for his study, which included questions on satisfaction with level of care, the information given to patients and their knowledge of medication. The questionnaire was used in both study groups. At 12 months follow-up, there was little difference in the level of satisfaction with the service provided between groups.

DISCUSSION

Summary of main results

We reviewed the results of 26 randomised controlled trials evaluating the effect of an integrated disease management (IDM) program in patients with COPD. All included studies contained a program provided by caregivers from at least two different disciplines, with two different components (for example exercise, education, self management etc) and with a duration of at least three months. Firstly, pooled data showed statistically and clinically relevant improvements in disease-specific quality of life on the CRQ in the IDM group: dyspnoea (MD 1.02; 95% CI 0.67 to 1.36); fatigue (0.82; 95% CI 0.46 to 1.17); emotional (0.61; 95% CI 0.26 to 0.95) and mastery (0.75; 95% CI 0.38 to 1.12). All domains (dyspnoea, fatigue, emotional and mastery) exceeded the minimum clinically relevant difference until 12 months follow-up. Only two studies measured long-term results on the CRQ, which showed that the positive effect was maintained for the fatigue, emotion and mastery domains at 24 months follow-up. Furthermore, disease-specific quality of life was also measured with the SGRQ. There was considerable heterogeneity in the score on the SGRQ. After multiple sensitivity analyses, we concluded that there was a difference in the SGRQ total score in favor of patients treated with IDM, which lies around the minimal clinically relevant difference of four units. The effect was greatest for the impact domain. We could not find a difference in the SGRQ total score at long-term follow-up. Remarkably, only two studies could provide data.

Second, the pooled data showed statistically significant improvements in maximal and functional exercise capacity, with an improvement of 7 Watts and 44 meters in favor of the IDM group, respectively. Sensitivity analysis of the 6MWD lowered the effect to 15 meters, indicating the likelihood of an overestimated effect in the lower quality studies.

Thirdly, the total number of patients with at least one respiratory-related hospital admission decreased from 27 per 100 to 20 per 100 patients in favor of the intervention group, with a number needed to treat of 15 patients to prevent one being admitted to hospital over three to 12 months. Mean hospitalisation days decreased on average by three days in the IDM group. The effects on the aforementioned primary outcomes are summarized in the Summary of findings for the main comparison. There was no evidence of an effect on generic quality of life, the number of patients with at least one exacerbation, the number of hospital admissions for all causes, emergency department visits, courses of antibiotics/prednisolone, dyspnoea, lung function parameters or depression scores.

Overall completeness and applicability of evidence

We found sufficient studies to address the objective of this review. All studies reported at least one primary outcome, and all studies were included in at least one pooled analysis. The COPD population in the included studies ranged from mild to very severe COPD and trials were conducted across all types of healthcare settings in a range of different countries. Although the results of this review appear therefore to be applicable to all COPD patients worldwide, one should bear in mind that applicability may depend on the context of available healthcare resources. The IDM programs included in this review differed in the type of health care providers involved, type of components and duration of intervention, reflecting the diversity of daily practice. Overall, programs containing at least two health care providers and two different elements, showed improvements in quality of life and exercise capacity, and reduced the number of hospital admissions and days spent in the hospital. We found no differences in quality of life and exercise tolerance between patients treated in primary or secondary care. Although the mean differences between groups were lower in studies using a mono-disciplinary treatment as a control group compared to usual care, the subgroup difference did not reach statistical significance. Furthermore, subgroup analysis on studies focusing mainly on exercise programs showed a statistically significant greater improvement in exercise capacity. Further research is required to define the optimal combination, intensity and duration of components in IDM programs.

Quality of the evidence

We included RCTs only and found 26 trials assessing almost 3000 participants. A priori, we intended to perform meta-analyses on some outcomes when feasible. However, with this amount of data we were able to perform pooled data analysis for all outcomes. As

a result of the complex intervention, there was a certain amount of clinical and statistical heterogeneity among studies. We have incorporated heterogeneity into the estimated effects by using random-effects analyses, where possible. Using the GRADE approach, we specified the levels of quality of the evidence (high, moderate, low and very low) in our 'Summary of findings' table. According to this approach, we checked if the included trials had limitations in terms of design, indirectness of the evidence, unexplained heterogeneity or inconsistency of the results, imprecision of the results or high probability of publication bias. If one of these factors was present, we downgraded the evidence. On the SGRQ, there was considerable variation in risk of bias between studies. Risk of bias tended to be lower in the more recently published trials compared to older trials. Sensitivity analyses based on studies with low quality did not change the direction, significance or magnitude of the effect. Therefore we concluded that the quality of the evidence was 'high'. For the CRQ, there were four studies which were all of moderate quality and presented with some form of bias, therefore we did downgrade the evidence to 'moderate' quality. We downgraded the evidence on functional exercise capacity for inconsistency, as substantial heterogeneity (I^2 = 84%) was present. After performing sensitivity analysis, the mean difference substantially decreased to 15 meters. We did not downgrade for respiratory-related admissions or hospitalisation days, as we feel the studies presented consistent, homogeneous results. We expect that additional trials with proper description of their methods and data collection could upgrade the quality of evidence and further our findings.

Potential biases in the review process

Several methodological strengths minimized the risk of bias in this review. As definitions of IDM are still under debate, we a priori strictly determined the inclusion criteria for an IDM program, which was published in our protocol. Our definition was derived from the definitions published in the literature (Peytremann-Bridevaux 2009; Schrijvers 2009). Overall, they reported on "multiple interventions, designed to manage chronic conditions, with a focus on a multidisciplinary approach". Furthermore, these definitions suggest that IDM interventions should "focus on maximum clinical outcome, regardless of treatment setting(s) or typical reimbursement patterns". As a result, we chose to include all interventions, independent of treatment setting, and to keep our definition as simple as possible, in order to be easily understandable for readers and easy to use for us as authors when checking on all relevant literature. Therefore, we restricted the inclusion of trials to multi-component, multidisciplinary programs of at least three months duration. Furthermore, we performed comprehensive searches to identify possible studies, leading to almost 4800 potentially relevant abstracts being identified. Subsequently, three different assessors assessed the abstracts. All studies that were excluded by two authors because of the type of intervention were triple-checked by a third review author to make sure all studies describing an IDM program were included. We reached consensus on all included studies. Although we followed the inclusion criteria for IDM as stated in our protocol, final decisions on the inclusion of studies are open to interpretation or criticism.

Limitations of this review include possible bias from inconsistent reporting of data from included studies. We requested additional data from 14 authors and received an answer from 11. Six of them could provide us with additional data, which could potentially have biased the results. Furthermore, only three out of 26 studies published a study protocol with which we could compare the results sections. In the other studies, we examined whether the outcomes reported in the methods section of the paper were reported in the results section. It is possible that this could have introduced bias if the authors blanked out outcomes from their methods section.

Lastly, there was heterogeneity present in the control group as we used a broad a priori definition of controls, varying from no treatment to treatment including one component of COPD care. We acknowledge the fact that controls and usual care differ between countries and between healthcare settings. Therefore, we performed subgroup analysis to investigate to what extent a difference between the control groups possibly influenced the results. From these analyses we concluded that the effect between intervention and control groups is less strong if patients in control groups receive one component of IDM compared to patients receiving no treatment or usual care.

Agreements and disagreements with other studies or reviews

This review adds to the results of four earlier systematic reviews analyzing IDM for COPD patients (Adams 2007; Niesink 2007; Peytremann-Bridevaux 2008; Lemmens 2009). The current review brings together new trials that were not included in any of these reviews. Some of these earlier reviews analyzed some of our primary outcomes. Adams 2007 examined the effectiveness of programs for COPD patients including chronic care model components and pooled six trials including at least two components. Pooled results did not demonstrate statistically significant differences on the SGRQ. Patients with COPD who received interventions with two or more chronic care model components had lower rates of hospitalisation and a shorter length of stay compared with control groups, comparable to our results. Lemmens 2009 examined the effectiveness of multiple interventions in asthma and COPD patients. The authors pooled data on the SGRQ from three studies in which two components of IDM were compared to usual care and three studies in which three components of IDM were compared to usual care. The effect on the SGRQ was larger if three components of IDM were used (MD -4.69; 95% CI -8.34 to -0.83 versus MD -0.95; 95% CI -4.23 to 2.34). Pooled data from

five studies showed a decrease in the number of respiratory-related hospitalizations, with a pooled OR of 0.58, which is comparable to the OR of 0.67 found in this review. Niesink 2007 evaluated quality of life in COPD patients, but did not perform a meta-analysis; reasons for this were not clearly described. Five out of 10 studies showed a clinically relevant improvement in quality of life. Peytremann-Bridevaux 2008 examined the effectiveness of IDM in COPD patients on exercise tolerance, quality of life, hospital admissions and mortality. Only data on hospital admissions and exercise tolerance were pooled. Positive effects on exercise capacity are in line with this review. The authors demonstrated a mean improvement of 32 meters on the 6MWD in five studies, which is comparable to our results. Furthermore, a pooled odds ratio of 0.85 (95% CI 0.54 to 1.36) for mortality is comparable to our review. Differences between this review and these other reviews are related to differences in the inclusion criteria for patients and the focus of programs. All reviews used different definitions of IDM; however there was some overlap with this review. Lemmens 2009 et al also based their definition on the EPOC list (EPOC 2008), whereas Adams 2007 and Steuten 2009 based their definition of IDM on the chronic care model as reported by Wagner 1996. The definition used by Peytremann-Bridevaux 2008 was similar to our definition, with the only difference being a duration of the intervention of at least 12 months instead of three months. Finally, all the aforementioned systematic reviews included study designs other than RCTs.

Our findings from the St. George's Respiratory Questionnaire (SGRQ) showed improvements of a similar magnitude to those reported in two recent Cochrane reviews evaluating two other supposedly important pharmaceutical cornerstones of COPD treatment, tiotropium (Karner 2012a) and inhaled corticosteroids (Yang 2012). IDM resulted in a higher MD on the SGRQ of -3.71 compared to the MD of tiotropium (-2.89); however, the confidence interval for IDM is wider (95% CI -5.83 to -1.59) compared to the confidence interval (95% CI -3.35 to -2.44) for tiotropium.

Eight studies in this review are also evaluated in a Cochrane review assessing the effectiveness of pulmonary rehabilitation (Lacasse 2006) and four studies included in this review are also evaluated in a Cochrane review assessing the effect of self management programs (Effing 2007). In line with the review of Effing 2007 (OR 0.64; 95% CI 0.47 to 0.89) we found a decrease in respiratory-related hospital admissions (OR 0.64; 95% CI 0.47 to 0.89). Furthermore, both reviews demonstrated improvements in disease-specific quality of life, although the effects tended to be higher and clinically relevant in the pulmonary rehabilitation review (Lacasse 2006), whereas in the self management review the improvement was too small to be of clinical relevance (Effing 2007). A priori we determined subgroup analyses on the type of dominant intervention in the program. Subgroup analysis of studies containing some form of exercise training showed greater improvement in quality of life, which exceeded the clinically relevant threshold on almost all domains. These results are in line with the Lacasse review. However, a subgroup analysis performed on studies that mainly focused on self management did not exceed the minimum clinically important difference, in line with the Effing review.

Furthermore, Effing 2007 and Lacasse 2006 reported pooled estimates for functional exercise capacity. Not surprisingly, as the focus in most included pulmonary rehabilitation studies lies on exercise training, the 6MWD improved significantly by 48 meters in the Lacasse review. This effect size is comparable to our overall estimate of 44 meters and our subgroup analyses on studies including an exercise program in which we found a mean difference of 50 meters. In contrast to these results, Effing did not find any significant differences in exercise capacity at all (weighted mean difference -6.25; 95% CI -24.05 to 11.05).

We did not find a difference between groups in the number of patients with at least one exacerbation. However, we concluded that there was a reduction in the number of patients admitted and the mean number of hospital days related to exacerbations. Self management education including the use of action plans might lead to more and better self treatment of exacerbations. As a result, hospital admissions will decrease (Effing 2007). In our included studies, a self management program caused patients to respond three days sooner on complaints (Trappenburg 2011). Furthermore, patients more often initiated treatment by themselves, which could then be successfully treated with oral steroids at an early stage (Sridhar 2008). As a result, perceived exacerbations were rated as substantially milder (Trappenburg 2011) and were less likely to result in an admission (Bourbeau 2003).

In the past few years, several systematic reviews evaluating IDM for various other chronic conditions have been published (Norris 2002; Badamgarav 2003; Gonseth 2004; Neumeyer-Gromen 2004; Knight 2005; Roccaforte 2005; Pimouguet 2010). Overall, quality of care improved with these programs, however some of the differences were in fact clinically modest (Peytremann-Bridevaux 2008). We found that the results of this review were most comparable to a systematic review evaluating patients with heart failure, which demonstrated that all-cause and heart failure-related hospitalisation rates were significantly reduced: OR 0.76 (CI 0.69 to 0.94, P < 0.0001) and OR 0.58 (CI 0.50 to 0.67, P < 0.0001), respectively (Roccaforte 2005). In studies evaluating depression and diabetes, differences in health care use and quality of care were less clear (Neumeyer-Gromen 2004; Knight 2005).

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis provides evidence for the efficacy of integrated disease management (IDM) programs of at least three months duration for chronic obstructive pulmonary disease (COPD) patients, for up to 12 months follow-up. We found positive effects

on disease-specific quality of life and exercise capacity in studies containing an exercise program, suggesting that exercise training is an important element in an IDM program. Long-term effects are still unclear, as only a few studies evaluated these. The magnitude of improvement in disease-specific quality of life was clinically relevant, especially using the Chronic Respiratory Questionnaire (CRQ).

We calculated that seven hospital admissions related to respiratory problems can be prevented for every 100 patients treated with IDM for three to 12 months, giving to a number needed to treat of 15 patients to prevent one being admitted. Furthermore, hospitalisation decreased by three days in patients treated with IDM compared to controls. This is of utmost importance, as hospitalizations contribute to the highest burden and costs in patients with COPD. The effects of IDM on the total number of patients suffering at least one exacerbation still remain unclear. It is possible that patients who have learned from education and have an action plan may recognize exacerbations at an early stage and can start medical treatment directly. It is therefore likely that further worsening of health status and hospital admissions can be prevented in these patients.

Implications for research

The following issues could be assessed if authors are planning future trials regarding the effectiveness of IDM:

1. Study quality: Overall, studies included in this systematic review were of moderate quality, as not all aspects of risk of bias were appropriately addressed. Therefore, there is a need for future trials to report a proper description of the processes of randomisation and data collection. Preferentially, a study protocol including measured outcomes should be published in advance to minimize selection and reporting bias.

2. More detailed description of intervention: A detailed description of the precise nature of the intervention is important, in order to be able to determine in the future which components, duration and intensity of a program are most effective. Ideally, we wish to determine which combination of health care providers and which components are most effective in IDM programs.

3. Consensus on reporting common outcomes: Given the huge variation in outcome measures and follow-up time points, we strongly recommend consensus on the reporting of common outcomes, such as change from baseline in health-related quality of life, in order to be able to combine more results in future meta-analyses. We advise future trial authors to measure at least one of the following outcomes: quality of life, exercise tolerance or exacerbation-related outcomes.

4. Adequate power calculation and methods of analysis: two cluster-randomized controlled trials introduced noteworthy bias due to inadequate methods of analysis, not taking the clustering into account (Rea 2004; Wood-Baker 2006) and loss to follow-up of clusters (Rea 2004). Therefore, we recommend performing a proper power calculation beforehand and, if needed, adjusting this calculation for intra-cluster effects (Guyatt 2011; Higgins 2011).

Finally, given the heterogeneity of interventions, there is a need to reach consensus on which interventions are likely to yield the best results when applying integrated care programs for COPD.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aiken 2006

Methods	RCT; follow-up: unknown; control group: usual care, which means patients receiving care from managed care organizations (MCO)
Participants	Eligible: 192 (COPD and congestive heart failure) Randomized COPD: 61 Mean age/sex: not reported for COPD patients Inclusion criteria: COPD or congestive heart failure patients, palliative treatment residing at home, receiving care by MCO, mean life expectancy of 2 years, saturation < 88%, oxygen usage, marked limitation of physical functioning, recent exacerbation
Interventions	Phoenix Care palliative intervention services were added to treatment services of local MCOs. Registered nurse case managers (serving 30 to 35 patients) provided the intervention service. These nurses worked with protocols and held contact with the attending physicians. Furthermore, they developed care plans, provided education to patients and tailored self management of the disease. They supported services including assessing psychological and spiritual needs. During exacerbation episodes, the nurses assessed medical status, implemented a symptom control intervention and contacted the physician Included health care providers (HCP): GP, nurse case manager
Outcomes	SF-36, medical utilization
Notes	Main component of program: structured follow-up with nurses/GP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out within diagnosis, in blocks of 30 patients (15 intervention, 15 control) by a member of the project administration staff."
Allocation concealment (selection bias)	Low risk	Quote: "Sealed-envelopes, colour-coded by diagnosis and containing the assignment to condition, were shuffled and assigned to participants in order of shuffling (..) the enroller, blinded to condition, opened the sealed envelope that identified the patients' study condition. "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation

Aiken 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All participants received an interview administered by a professional interviewing firm; interviewers were blind to condition and diagnosis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors performed an attrition analysis according to the Jurs and Glass procedure
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bendstrup 1997

Methods	RCT; follow-up: 24 weeks; control group: no treatment
Participants	Eligible: 47 Completed: 32 Mean age I: 64 yrs, C: 65 yrs Sex (% male) both groups: 56% Inclusion criteria: diagnosis of COPD according to GOLD, FEV1 of 25% to 55% of predicted value, Tiffeneau index less than 70%, stable condition for 4 weeks (no change in exercise status, sputum color/quantity, no change in medication) Major exclusions: heart disease, musculoskeletal disease limiting exercise, intermittent claudication limiting exercise
Interventions	12 week program including: - Exercise training (strength training, backwards/sideways walking, endurance training): 3 times per week for 1 hour during 12 weeks. Patients were encouraged to train at home - Occupational therapy: 2 group sessions - Education: 12 sessions, including proper administration, inhalation techniques, psychological education, socioeconomic problems and nutrition - Smoking cessation: free nicotine patches, education Included HCP: practice nurse, physiotherapist, dietician, psychologist, occupational therapist, social worker, physician
Outcomes	Chronic Respiratory Disease Questionnaire (CRDQ), York Quality of Life Questionnaire (YQLQ), 6MWD, lung function, patient attendance, staff working hours
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to either an intervention or a control group"; no information on allocation procedure provided

Bendstrup 1997 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The methods used to conceal the sequence of treatment group allocation were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We could not ascertain how and whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	High drop-out rate (31%) and no intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Bourbeau 2003

Methods	RCT; follow-up: 12 months; control group: usual care
Participants	Eligible: 469 Randomized: 191 Completed: 165 Mean age: I: 69 yrs; C: 70 yrs Sex (% male): I: 52%; C: 59% Inclusion criteria: stable COPD with at least one hospitalisation for an exacerbation in preceding year, age $\geq$ 50 yrs, pack yrs $\geq$ 10 yrs, FEV1% predicted (post-bronchodilator) : 25% to 70%, FEV1/VC < 70% Major exclusions: no previous diagnosis of asthma or left congestive heart failure, terminal disease, dementia, uncontrolled psychiatric disease, no pulmonary rehab < 1 yrs ago, no long-term facility stays
Interventions	A disease-specific self management program (Living Well with COPD) of 7 to 8 weeks of follow-up including: - Individual sessions of education by an experienced health professional at the patient's home - Content of education: COPD knowledge, breathing and coughing techniques, energy conservation during day-by-day activities, relaxation exercises; preventing and controlling symptoms through inhalation techniques, understanding and using a plan of action for acute exacerbation, adopting a healthy lifestyle, leisure activities and travelling, a simple home exercise program and long-term home oxygen therapy - An action plan for acute exacerbations was customized for each patient Intensity: education 1 hour per week during 7 to 8 weeks, follow-up first 2 months weekly telephone calls, then once a month a telephone call. Exercise evaluation (not

	mandatory): 3 times per week, 30 to 45-min/session + exercise teaching Included HCP: nurse, physiotherapist, physician, pulmonologist	
Outcomes	SGRQ, exacerbations, spirometry, FEV1 (L), forced vital capacity, hospital admissions, symptoms, emergency room visits, outpatients visits, 6MWT, walking distance	
Notes	Main component of program: self management (including action plan)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients underwent randomisation with the use of a central computer-generated list of random numbers. Randomization was stratified per centre and in blocks of 6, and patients were assigned to the self management program (intervention group) or to usual care."
Allocation concealment (selection bias)	Low risk	Quote: "The blocking factor was not known by the investigators or their staff in each participating centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Since a double-blind design was impossible ..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ".. an independent evaluator unaware of the patient assignment was responsible for the evaluation process in each centre. The evaluator was cautioned not to ask about the workbook modules and types of contact"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "An intention to treat analysis included all available study patients"
Selective reporting (reporting bias)	High risk	Data on the 6MWD not presented, but only stated as "not statistically significant", and authors can not provide us with additional data

Boxall 2005

Methods	RCT; follow-up 12 weeks; control group: usual care
Participants	Eligible: not clear Randomized: 60 Completed: 46 Mean age I: 78 yrs; C: 76 yrs Sex (% male): I: 48%; C: 65% Inclusion criteria: diagnosis of COPD by a respiratory specialist, age > 60 yrs, dyspnoea on exertion, live locally, motivated to exercise daily unsupervised, stable for 2 weeks, functionally housebound Major exclusions: attending outpatient based PR, restricted shoulder movement, living in nursing home, previous lung volume surgery, pain limiting mobility
Interventions	12 week program including: - Exercise consisting of walking (level 1 to 10) and arm exercises (1 to 18) + education sessions. Patients were required to carry out exercise daily. Weekly physiotherapy visits were scheduled for the first 6 weeks, and then visits were made until week 12 of the program. Visits were used to monitor exercise performance, progress exercises, retest 6MWT at regular intervals (weeks 1, 4, 6, 8 and 12 of the program) and provide encouragement to patients - Educational sessions for patients and carers were conducted by physiotherapists, nurses and occupational therapy staff in their homes. Those sessions covered: anatomy and physiology of the lungs, use of respiratory devices, medications, breathing techniques, secretion removal techniques, energy conservation, use of adaptive aids and stress management. Patients received on average 11 home visits during the program Included HCP: physiotherapists, nurses, occupational therapist
Outcomes	Health status: SGRQ, 6MWD, hospital admissions, average length of stay, dyspnoea Borg Scale
Notes	Main component of program: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to equal groups using computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Random number were coded into opaque envelopes by a person independent from the study, they retained the envelopes until initial assessment was completed."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither assessors nor participants were blinded to group assignment in this study"

Boxall 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Neither assessors nor participants were blinded to group assignment in this study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers (23/23 analyzed in both groups) across intervention and control group, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Cambach 1997

Methods	RCT with cross-over design; follow-up 6 months; control group: drug treatment only
Participants	Eligible: 89 (asthma and COPD) Analyzed: 23 (COPD) Mean age I : 62 yrs, C: 62 yrs Sex (% male): I: 47%, C: 75% Diagnosis of asthma or COPD according to guidelines, evidence of dyspnoea and decreased exercise tolerance as a result of obstructive lung disease, 18 to 75 yrs, ability to travel independently to the physiotherapy practice, medication prescribed by a pulmonary physician, motivation to improve self care, informed consent Major exclusions: 1) manifest cardiac complaints, 2) hypercapnia and/or hypoxia
Interventions	12 weeks intervention including: Exercise group sessions of 3 to 4 participants including techniques of breathing retraining and evacuation of mucus, exercise training, patient education, relaxation techniques and recreational activities. Training was 3 days a week for 90 minutes. Exercise training was performed twice a week on a cycle ergometer and by stair-walking. Recreational activities were once a week for 45 min. Education sessions were every week for 45 min Included HCP: nurse, physiotherapist
Outcomes	6MWT, incremental cycle ergometer test, CRQ
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "block randomisation procedure; four closed envelopes for condition RC and four closed envelopes for condition CR"

Cambach 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Four closed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors not likely to have been blinded to intervention, as patients were tested for exercise capacity in their practices, by their treated physiotherapist, who was probably not blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Data obtained from patients who did not return for one or more of the assessments (i.e. baseline (t0), after 3 months (t3) and/or after 6 months (t6), or patients who were not measured within 3 weeks (from t0, t3 and t6) were excluded from data analysis". Comment: exclusion of non-responders may have affected outcome data
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Dheda 2004

Methods	RCT; follow-up 6 months; control group: primary care follow-up
Participants	Eligible: 33 Completed: 25 Mean age I: 68 yrs, C: 71 yrs Sex (% male) both groups: unknown Diagnosis COPD according to British Thoracic Society guidelines, patients with a first admission to hospital, with progressive symptoms, a smoking history of > 20 pack-years Major exclusions: another dominant medical condition, a mandatory reason for hospital follow-up
Interventions	Intervention program of 6 months A respiratory nurse and/or chest physician reviewed the intervention group at least 4 times in the 6 month period (at 6, 8, 12 or 16 weeks). The following interventions were made at some or all of these visits: spirometry with reversibility, review of inhaler technique and peak flow diary, ambulatory oxygen assessment, smoking cessation advice, steroid trial, nebuliser assessments, review of medication, advice about nutrition and exercise, and introduction to a patient support group Included HCP: nurse, chest physician

Dheda 2004 (*Continued*)

Outcomes	SGRQ, SF-36	
Notes	Main component of program: structured follow-up with nurse/GP	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	The methods used to conceal the sequence of treatment group allocation were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blind to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported and therefore unclear who scored outcome assessments (patients, caregivers, outcome assessors?)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether the results in SGRQ were described in the total population, as well as in the patients who withdrew (n = 8) from the study
Selective reporting (reporting bias)	High risk	Not all outcome measurements are given in measures but only reported as "there was no significant difference at 6 months in FEV1"

Engstrom 1999

Methods	RCT; follow-up 12 months; control group: usual outpatient care
Participants	Eligible: 58 Randomized: 55 Completed: 50 Mean age I: 66 yrs, C: 67 yrs Sex (% male) I: 54%, C: 50% Clinical diagnosis of COPD, developing after at least 10 yrs of smoking, FEV1 < 50%, debut of symptoms after 40 yrs of age, dyspnoea mainly elicited by exercise or infections, no allergy Major exclusions: disabling or severe diseases, co-existence of other causes of impaired pulmonary function

Engstrom 1999 (*Continued*)

Interventions	12 months rehabilitation program including: - Exercise training sessions (bicycle, arm and breathing techniques), 2/week for 6 weeks, once weekly for 6 weeks, once every second week for 6 weeks and then once a month for remaining period. Every session: 45 min. Furthermore, instructions for daily walks and an individualized daily 30-min home-training program - Individualized educational program with outpatient team (nurse and physician) on visit every 3 months - Occupational therapist gave 2 group sessions about energy saving techniques and 2 global education sessions - Dietician gave information about nutrition in COPD patients and intervened in mal-nutrition Included HCP: physiotherapist, nurse, physician, dietician, occupational therapist
Outcomes	SGRQ, 6-MWD, W-max, days in hospital, SIP, Mood Adjective Check List (MACL)
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	High risk	Quote: "Patients with COPD were recruited consecutively and, when a sufficient number had been collected, randomised to produce a rehab group and a control group of equal size."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All the physiological and QOL assessments were blinded, except the walking test, which was performed by the nurse in the rehabilitation team"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention and control group (2 versus 3 persons)
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Farrero 2001

Methods	RCT; follow-up 12 months; control group: usual care
Participants	Randomized: 122 Completed: 94 Mean age I: 69 yrs, C: 69 yrs Clinical diagnosis of COPD, requiring oxygen for at least 6 months, with willingness to participate in a hospital based home-care program, and with residence within easy reach of the hospital
Interventions	Hospital based home-care program of 12 months with the aim of combining home-care management and easy access to hospital resources. Program included: - Monthly telephone calls and 3-monthly home visits from a nurse, working closely with a physician. Patients could also request with an immediate response, which varied according to a home visit, a hospital visit, telephone advice or a control visit. Included HCP: nurse and physician
Outcomes	CRQ, spirometry, mortality, hospital admissions, hospital days, ED visits
Notes	Main component of program: structured follow-up with nurses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After this initial evaluation, informed consent was obtained and patients were allocated randomly to the HCP treatment group or to the control group". Comment: unclear if patients were randomised by sequence generated or based on, for example, date of admission
Allocation concealment (selection bias)	Low risk	Quote: "Codes of randomisation were kept in sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients in the control group were evaluated by the HCP team at the outpatient department in the initial visit, and after 1 year." Comment: as the HCP team was the intervention team and was not blinded to which group a patient was randomised, it is likely that assessment can be influenced by no blinding of the outcome assessor

Farrero 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Quality of life was investigated in the first 40 consecutive patients included in the study (..) applied before the study and after 3 months and 12 months." Comment: reason for missing outcome data likely to be related to true outcome, with imbalance in numbers
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Fernandez 2009

Methods	RCT; follow-up 12 months; control group: education (mono-disciplinary intervention)
Participants	Eligible: 50 Randomized: 50 (I: 30; C: 20) Mean age: 66 yrs, C: 70 yrs Sex: 100% male (both groups) Inclusion criteria: GOLD 4 patients, younger than 80 yrs of age, stable COPD, defined as a period of 2 months without any exacerbations, defined as signs of acute dyspnoea requiring medical attention, changes in the quantity and characteristics of sputum, an increase in pulmonary noise or an increase in the necessity for medication, the correct administration of pharmacological treatment according to GOLD, home treatment with oxygen for at least 6 months prior to the commencement of the study Major exclusions: severe cardiovascular pathology, unstable angina, acute myocardial infarction, cerebral vascular accident, or physical or psychological disorder that impede the practice of physical exercise
Interventions	Rehab program of 11 months At the start: 2 one-hour sessions of respiratory re-education in the hospital, where exercises at home were taught Home-rehab program : - 1 hour of exercise per day (respiratory reeducation, muscular inspiratory training, muscular training of upper and lower limbs) - First 2 months: attendance of physiotherapist at home (who visited twice monthly for 1 hour) - Month 2 to 9: single monthly visits physiotherapist, included resistance training, respiratory reeducation, isotonic training, training of respiratory muscles - 3 respiratory education sessions by nursing staff (handling of inhalers, knowledge of the illness, what to do in the event of attack) Included HCP: nurse, physiotherapist
Outcomes	Pulmonary function, SGRQ, 6MWD
Notes	Main component of program: exercise

Fernandez 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "50 patients were prospectively randomised to block of 5 patients and randomly divided into 2 groups."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates between groups comparable
Selective reporting (reporting bias)	Low risk	All outcomes in methods section provided

Gottlieb 2011

Methods	RCT; follow-up: 18 months; control group: usual care
Participants	Eligible: 133 Randomized: 61 Completed: 26 Mean age I: 74 yrs, C: 73 yrs Sex (% male): I: 32%, C: 35% Inclusion criteria: a diagnosis of moderate COPD, FEV1/FVC < 0.7 and 50% ≤ FEV1 < 80% with motivation for pulmonary rehabilitation Exclusion criteria: 1. Co-morbidity contraindicating rehabilitation 2. Participation in PR within the last year 3. Cognitive disorders limiting the ability to participate in physical training and educational sessions
Interventions	Program of intensive training for 7 weeks, with maintenance program for 6 months, including: - Intensive 7-week physical training and educational phase led by a multidisciplinary team. Furthermore, smoking cessation counseling given on an individual basis and a dietary intervention consisted of group cookery classes and individual sessions - Final interview following completion of the program, in which participants' achievements were compared to the original goals - Maintenance program for 6 months, including a 90-min monthly session focusing on

Gottlieb 2011 (*Continued*)

	ways of incorporating exercise in daily life, and 2 sessions on exercise activities in the local community, and another 2 sessions on exercise as well as on repetition of relevant topics Included HCP: multidisciplinary team, not further specified. Authors were unreachable for further information
Outcomes	SGRQ, 6MWD, MRC, Borg dyspnoea scale, Sit-to-Stand test
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised 1:1 to pulmonary rehabilitation and control"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using sealed opaque envelopes randomly assigned to participants"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We could not ascertain how and whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate equally divided: 39% intervention group, 23% control group
Selective reporting (reporting bias)	High risk	Results on MRC Dyspnea Scale not reported in results section

Güell 2000

Methods	RCT; follow-up: 24 months; control group: usual care
Participants	Eligible: 65 Randomized: 60; I: 30, C: 30 Completed (24 months): 47 (I: 23; C: 24) Mean age I: 66 yrs, C: 64 yrs Sex (% male) both groups: 100% Inclusion criteria: age $\leq$ 75 years, FEV1 < 70%, FEV1/FVC < 65%, PaO2 > 55 mm Hg at rest with no indication for prescribing home oxygen therapy Major exclusion criteria: clinically apparent heart disease, bone or joint disease Exacerbation or hospitalisation in previous month

Interventions	6 months intensive rehabilitation program, followed by a 6-month maintenance program - First 3 months: 2 30-min sessions each week: breathing retraining, combined with a low-level home exercise program. If indicated, patients also received chest physiotherapy, which involved teaching effective cough and postural drainage. Patients attended educational sessions on the anatomy and basic physiology of the respiratory system as well as on the nature of their disease and of PR - Month 3 to 6: exercise training program of 5 30-min sessions weekly on a stationary cycle ergometer. During this period, patients also began a program of home exercise with either 30 min of pedaling on a stationary cycle or 1 h of walking - Month 6 to 12: single weekly session in groups during which they performed exercises for breathing and leg-arm co-ordination - Month 12 to 24: instructed to do home exercises without supervision Included HCP: nurse, physiotherapist, pulmonologist
Outcomes	Lung function, 6MWD, cycle ergometer, VAS, MRC, CRQ, exacerbations, hospital admissions
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done at inclusion of consecutive patients"
Allocation concealment (selection bias)	High risk	Quote: "Randomization was not concealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "same physician saw patients at each visit". It was unlikely that the health care professional was blinded to treatment group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The technicians, who collected data for outcome measures at every visit, as explained below, were blinded to a patient's allocation to PR or control groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Güell 2006

Methods	RCT; follow-up: 4 months; control group: usual care
Participants	Randomized: 40; I: 20; C: 29 Completed: 35; I: 18, C: 17 Mean age: I: 68 yrs, C: 66 yrs Male: I: 88%, C: 100% Inclusion criteria: age ≤ 75 years, FEV1 < 70%, FEV1/FVC < 65%, PaO2 > 55 mm Hg at rest with no indication for prescribing home oxygen therapy Exclusion criteria: psychiatric disturbances, no heart, bone or joint disease. Exacerbation or hospitalisation in previous 2 months
Interventions	PR program of 4 months, including: - First 2 months: 2 30-min sessions each week, including relaxation techniques, breathing retraining, and chest wall and abdominal muscle wall work. Patients attended 4 45 to 60-min educational sessions - Month 2 to 4: 5 30-min sessions weekly exercise training on cycle ergometer Included HCP: nurse, physiotherapist, pulmonologist
Outcomes	Millon Behavior Health Inventory (MBHI), Revised Symptom Checklist (SCL-90-R), 6MWD, CRQ
Notes	Main component of program: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done at inclusion of consecutive patients" Comment: it is not clear how the sequence was generated
Allocation concealment (selection bias)	High risk	Quote: "Randomization was not concealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither patients nor clinicians were blinded to allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the technicians who collected the data were blinded to patient allocation, as were the data analysts until the analysis was deemed complete"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up comparable between groups (2 versus 3)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Koff 2009

Methods	RCT; follow-up 3 months; control group: usual care
Participants	Eligible: 40; randomised: 40; completed 38 Mean age I: 67 yrs, C: 65 yrs Sex (% male): I: 45%, C: 50% Inclusion criteria: clinical diagnosis of COPD, GOLD 3+4, with a telephone land line Exclusion criteria: active treatment for lung cancer, illiteracy, non-English speaking, inability to complete a 6MWD
Interventions	3-month intervention program, including: - Disease-specific education, by respiratory therapist at enrolment and daily by Health Buddy System (tele healthcare) Education included disease description, medications and their use, nutrition, breathing techniques - Teaching of self management skills (use of an oximeter and increased awareness of clinical changes/problems). Patients could contact the co-ordinator in case of deterioration - Patients were remotely monitored 5 days per week with the Health Buddy system for change in symptoms, saturation, 6MWD and lung function. The study co-ordinator reviewed these results and patients were contacted if they were at high risk for exacerbation. They started exacerbation management or had contact with respiratory physician/GP Included HCP: physician, pulmonologist
Outcomes	SGRQ, 6MWD, exacerbations, hospitalizations, ED visits, equipment satisfaction, number of calls
Notes	Main component of program: self management

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients randomly selected their group assignment (by choosing a blinded envelope that contained a group indicator"
Allocation concealment (selection bias)	Low risk	Quote: "patients randomly selected their group assignment (by choosing a blinded envelope that contained a group indicator"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because of the type of intervention, it was not possible to blind the subjects or investigators as to whether they were randomised to the treatment or control arms of the trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "primary end-point was collected by the coordinator, and analysed by R.H. Jones." The co-ordinator was also responsible for the intervention and was therefore

Koff 2009 (*Continued*)

		not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates balanced in numbers across groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Littlejohns 1991

Methods	RCT; follow-up 12 months; control group: usual care
Participants	Eligible: 166 Randomized: 152; I:73, C: 79 Completed (12 months): 133; I: 68, C: 65 Mean age I: 63 yrs, C: 63 yrs Sex (% male): I: 67, C: 63 Inclusion criteria: COPD diagnosed by spirometry, according to guidelines. Inclusion criteria: age 30 to 75 yrs, prebronchial FEV1 % < 60%, stable state, no change in medication for at least 6 weeks before recruitment, no other major disease
Interventions	Intervention group received the care of the respiratory health worker while continuing with their routine outpatient appointments during 12 months. The health worker provided: - Health education directed at the patient and the primary care team - Monitoring of treatment compliance and optimizing treatment by ensuring correct inhalation techniques and supervision of domiciliary oxygen - Monitoring of the results of spirometry and the patients's symptoms to enable acute exacerbations and worsening heart failure to be detected and treated early - Liaison between GP and hospital-based services (including domiciliary physiotherapy services and social services) Included HCP: GP, respiratory health worker
Outcomes	Mortality, spirometry, 6MWD, step test, MRC chronic bronchitis questionnaire, HADS, SIP, hospital admissions, drug prescriptions, visits to GP or clinic, satisfaction
Notes	Main component of program: structured follow-up with respiratory health worker

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random numbers were generated by tables in permuted blocks of four, stratified by age and sex"
Allocation concealment (selection bias)	Low risk	Quote: "the groups to which successive patients were to be allocated were noted in sealed, numbered envelopes, which were

Littlejohns 1991 (*Continued*)

		kept centrally"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the physician was aware which group the patient was in"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates comparable between groups
Selective reporting (reporting bias)	High risk	The outcomes on the MRC chronic bronchitis questionnaire are not reported

Mendes 2010

Methods	RCT; follow-up 12 weeks; 2 intervention groups (at home PR versus outpatient PR), 1 control group: usual care
Participants	Eligible: 117 Randomized: 117 (Intervention I: 42; Intervention II: 46; Control: 29) Analyzed: 85 (Intervention group I: 33; Intervention II: 23; Control: 29) Mean age: Intervention I: 66 yrs, Intervention II: 71, Control: 71 Sex (% male): Intervention I: 82%, Intervention II: 83, Control: 66% Inclusion criteria: diagnosis of COPD according to GOLD, stable at inclusion Major exclusions: hospitalisation or COPD instability, presence of neuromuscular disease, associated respiratory disease, orthopedic or neurological disease that affected gait, recent impairment due to co-morbidities, such as myocardial infarction, heart failure, stroke or neoplasm; prior pneumonectomy or other thoracic surgery
Interventions	Intervention program of 3 months performed either at home or at the outpatient clinic: - Both intervention groups received 1 session of education about COPD, treatment and relevance of PR - Both intervention groups trained 3 mornings a week for 3 months, with aerobic and strengthening exercises. Patients in the outpatient clinic trained under supervision; patients who trained at home were instructed in the clinic and received support by telephone calls Included HCP: physiotherapist, pulmonologist
Outcomes	6-MWD, MRC, FEV1, BMI, all included in BODE index (body mass, obstruction, dyspnoea, exercise tolerance- index)
Notes	Main component of program: exercise
Risk of bias	

Mendes 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised electronically by a computer"
Allocation concealment (selection bias)	High risk	Distribution of patients was unequal: 42 in at-home group, 46 in outpatient group versus 29 in control group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Two duly trained health care professionals were responsible for the evaluations, which were performed by the same evaluators for all patients". Comment: not clear if these professionals were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "19 out of 46 of out-patient intervention group were lost to follow up, compared to 7 out of 42." Comment: the reasons for missing outcome data likely to be related to true outcome, with imbalance in numbers of missing data
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Rea 2004

Methods	Cluster RCT; follow-up: 12 months; control: conventional care
Participants	Eligible: 158 Randomized: 135; I: 83, C: 52 Completed: 117 Mean age of both groups: 68 yrs Sex (% male) of both groups: 41.5% Inclusion criteria: COPD diagnosed by ICD-9-CM codes and GP records for a clinical diagnosis of moderate to severe COPD Major exclusion criteria for patients: chronic asthma, bronchiectasis, comorbidity more significant than COPD, unable to give informed consent, prognosis < 12 months, long-term oxygen therapy or too unwell, deceased Major exclusion criteria GP: no longer enrolled with participating GP practice or moved

	out of area, unable to contact patient, insufficient practice nurse resource
Interventions	A chronic disease management program was implemented including: - An action plan, which was implemented by patient's own GP and practice nurse, with advice from the respiratory nurse and specialist physician. The plan comprised a timetable for regular maintenance checks and set achievable goals for lifestyle changes - Patients visited the nurse monthly, the GP 3 monthly and at other times if worsening symptoms demanded more visits - Patients received education about smoking cessation, medication. Annual influenza vaccination and pulmonary rehabilitation were recommended Included HCP: GP, nurse, pulmonologist
Outcomes	Health status, SF-36, CRQ, shuttle walk test, spirometry, hospital admissions, medication, courses of oral steroids, courses of antibiotics, smoking cessation Randomization at cluster level, analysis at patient level
Notes	Main component of program: self management/action plan and structured follow-up by GP/nurse

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Practices were randomised, using a set of computer-generated numbers"
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and health care providers not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	The health care providers involved in the program administered outcome measurements at visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced between groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All outcomes reported
Recruitment bias	Low risk	Quote: "Written information about the trial was provided to patients and consent was obtained before patients knew whether they belonged to an intervention or control practice"

Rea 2004 (*Continued*)

Baseline imbalance between groups	High risk	No stratified or pair-matched randomisation was used, resulting in baseline imbalance of 99 eligible patients in the intervention group and 59 patients in the control group
Loss to follow-up of clusters	High risk	Quote: "After randomisation, two practices declined to participate and in three, changes of either GP's or practice nurses prevented participation before enrolment had begun"
Adequate analysis methods for CRT	High risk	Inadequate methods of analysis: randomisation done at level of GP practice, analysis performed at level of patients

Rice 2010

Methods	RCT; follow-up 12 months; control: single intervention (one page of information and telephone number)
Participants	Eligible: 743 Randomized: 743; I: 372, C: 371 Completed: 743 Mean age I: 69 yrs, C: 71 yrs Sex (% male) I: 98%, C: 98% Inclusion criteria: COPD diagnosed by spirometry. Inclusion criteria: at high risk for hospitalisation as predicted by one or more of the following during the previous year: hospital admission or ED visit for COPD, chronic home oxygen use, or a course of systemic corticosteroids for COPD Major exclusion criteria: any condition that might preclude effective participation in the study or that would reduce life expectancy to less than a year, or no access to a telephone
Interventions	Chronic disease management program of 12 months, including: - Group session (1-1, 5-hour): general information about COPD, medication, smoking cessation, vaccinations and exercise - All patients received an individualized written action plan including prescriptions for prednisone and antibiotics with contact information with a case manager. Participants were in possession of action plan medications at all times and were to refill prescriptions immediately upon initiating the action plan - The case manager made monthly telephone calls Included HCP: case manager, pharmacist
Outcomes	ED and hospital admissions related to COPD, SGRQ, mortality, number of telephone contacts
Notes	Main component of program: self management/action plan

Rice 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We assigned subjects in equal proportions to each of the two treatment arms by permuted Block randomisation"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded pulmonologists independently reviewed all discharge summaries and ED reports and assigned a primary cause for each"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported. Concordance between outcome observers was tested in subset and was 96.5%
Selective reporting (reporting bias)	Low risk	No missing outcome data

Smith 1999

Methods	RCT; follow-up 12 months; control: usual care
Participants	Eligible: 105 Randomized: 96; I: 48, I: 48 Completed: 36 (data only completed in Intervention group) Mean age I: 70 yrs, C: 70 yrs Major inclusion criteria: COPD diagnosis according to guidelines, age > 40 years, FEV1/FVC less than 60%, in a stable state, have a carer involved in their management, be able to speak and read English and give written consent Major exclusion criteria: no other active illness
Interventions	An intervention of 12 months including: - Follow-up planning of in- and outpatients with a nurse in shared care approach with GP and medical staff. Goals for discharge and nurses discussed with the GP the needs and facilitated involvement of domiciliary service. Goals were inserted into patients' notes - During 12 months every 2 to 4 weeks there was a home visit including education, spirometry, optimal medication, exacerbation management, smoking cessation and fitness advice Included HCP: nurse, GP, social worker, hospital medical officer
Outcomes	COOP (HRQoL), mortality, hospital admissions, lung function

Smith 1999 (*Continued*)

Notes	Main component of program: structured follow-up with nurses/GP	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised as they were enrolled, following discharge from hospital (..), into the HBNI or control groups from two lists of randomly computer generated numbers"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomised as they were enrolled, following discharge from hospital"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study was unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "This study was unblinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Attempts to perform questionnaires in the control subjects were unsuccessful due to a combination of (I) these subjects perceived no immediate benefit of the trial; and (ii) the burden of participating in a study" Comment: no outcomes reported in control group
Selective reporting (reporting bias)	High risk	One or more primary outcomes in the review (COOP, spirometry) are reported incompletely so that they cannot be entered in a meta-analysis

Sridhar 2008

Methods	RCT; 104 weeks; control group: usual care
Participants	Eligible: 297 Randomized: 122 (I: 61; C: 61) Mean age both groups: 70 yrs Sex (% male): both groups: 49% Inclusion criteria: diagnosis of COPD and admitted between 2000 and 2004 with an acute exacerbation of COPD

	Exclusion criteria: significant comorbidity (severe heart disease or cancer, or any condition that would preclude participation in the physical therapy component of a PR program)
Interventions	Intervention program of 24 months: - Patients started with a PR program for 4 weeks, including general education about disease and treatment, and physical training program - After 4 weeks, patients received a home visit, including a written COPD action plan for exacerbations. The GPs provided medication - Patients received monthly telephone calls and a home visit every 3 months until 24 months follow-up. They reinforced advice regarding treatments, smoking cessation, the need to continue their exercise therapy and reinforced the self management education Included HCP: GP, nurse, physiotherapist
Outcomes	CRQ, mortality, exacerbations, hospital admissions, lung function
Notes	Main component of program: exercise + action plan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "122 patients were suitable and were recruited and randomised by the use of random numbers to the intervention and control group"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates comparable between groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Strijbos 1996

Methods	RCT; 18 months; intervention group 1: hospital based PR, intervention group 2: home based PR, control group: usual care
Participants	Eligible: 50 Randomized: 50; I group 1: 18, I group 2: 17, C: 15 Completed: 41 Mean age I 1: 61 yrs, I 2: 60 yrs, C: 63 Sex (% male): I 1: 93%, I2: 80%, C: 80% Inclusion criteria: diagnosis COPD as evidenced by history, physical examination, chest radiograph and pulmonary function test results, PaCO2 at rest of less than 6.5 kPa, and PaO2 at rest of more than 7.5 kPa; FEV1 < 65% predicted Major exclusion: ischaemic heart disease, musculoskeletal disorders or other disabling diseases that could restrict the rehab therapy
Interventions	12-week rehabilitation program: - Both groups: exercise twice a week during 12 weeks, 1 hour each session - In the hospital group exercise was administered by a physiotherapist (1 hour twice a week) and patients were instructed to practice daily exercise for at least 15 min. Patient education 3 times/1 hour by a respiratory nurse - In the home-care group, exercise was carried out at home by the local physiotherapist and home-care nurse, under supervision of the GP. Patients received an individualized exercise program from physiotherapist of 30 minutes (24 sessions), and were instructed to exercise at least 15 to 30 min. They received 3 times education by a nurse and 3 times a visit by the physician or GP - Both groups were intended to continue exercise daily at home, after completion of the program Included HCP: nurse, physiotherapist and GP or pulmonologist
Outcomes	4minute walking test (4MWT), cycle test (measured as maximum watts, W-max) and interviews
Notes	Main component of program: exercise

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned to intervention or control group". Information is insufficient to be confident that the allocation sequence was genuinely randomised
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation

Strijbos 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We were unable to ascertain whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comparable low drop-out rates in both groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Theander 2009

Methods	RCT; 3 months; control group: usual care
Participants	Eligible: 30 Randomized: 30; I:15, C:15 Completed: 26 Mean age I: 66; C: 64 yrs Sex (% male): I: 25%; C: 71% Inclusion criteria: diagnosis of COPD: according to British guidelines, with FEV1 between 60% to 25% post bronchodilation, and age ≤ 75 yrs Major exclusions: disabling or severe disease other than COPD, impaired pulmonary function due to other disease, long-term oxygen therapy, alpha1-antitrypsine deficiency, cancer disease, untreated obstructive sleep apnea syndrome and no COPD-related symptoms affecting their activities of daily life
Interventions	Multidisciplinary program: - Physiotherapy 2 days per week (1 hour) for 12 weeks, with additional home training after q month - Dietician support (3 sessions of 1 hour): education and, if needed, additional nutritional supplementation - Occupational therapist: education and teaching - Nurse (two sessions of 1 hour): education and self care advice Included HCP: physiotherapist, dietician, occupational therapist, nurse
Outcomes	BMI, FEV1, fatigue impact scale, 6MWD, grip strength, SGRQ, SF-36
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "For the randomisation we prepared 80 sealed opaque envelopes with as-

Theander 2009 (*Continued*)

		signment information: 40 for the rehabilitation group and 40 for the control group"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization procedures were performed by an independent person from the research group, who took a random envelope from the prepared box with sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The data collection was performed by members of the rehabilitation group. The data collection was not blinded to the data collector"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comparable drop-out rates
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Trappenburg 2011

Methods	RCT; follow-up 6 months; control group: usual care
Participants	Eligible: 391 Randomized: 233, I: 111, C: 122 Completed (6 months): 193; I: 91, C: 102 Mean age: I 66 years, C: 65 years Sex (% male): I: 65% C: 69% Inclusion criteria: COPD diagnosed by spirometry, age > 40 years, smoking history of > 20 years or 15 pack-years, diagnosis of COPD as a major functionally limiting disease, current use of bronchodilator therapy Major exclusions: primary diagnosis of asthma, primary diagnosis of cardiac disease, presence of disease that could either affect mortality or participation in the study
Interventions	6-month self management/action plan program: - Individualized action plan with treatment prescriptions related to a color-coded symptom status to enhance an adequate response to periods of symptom deterioration - The action plan included ongoing support of a case manager, in concordance with a GP/respiratory physician. There were 2 reinforcement sessions by telephone at 1 and 4 months Included HCP: GP, nurse, pulmonologist

Trappenburg 2011 (*Continued*)

Outcomes	Exacerbation rates and recovery time, SGRQ, HADS, courses of antibiotics, corticosteroids, ED visits for exacerbation, CCQ score during exacerbation	
Notes	Main component of program: self management/action plan	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out using the minimization technique to balance the control and intervention groups for centre and gender"
Allocation concealment (selection bias)	Low risk	Quote: "to conceal the assignment sequence, a central web-based service was used"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "an informed consent to postponed information procedure is used, keeping the patient unaware of the AP being the major study aim. This implies that all patients are informed about the fact that, besides the outcome assessment aiming at gaining more insight in daily symptom variations, the study has another purpose. Patients are told that they will be informed about this additional research question only after follow up because informing during recruitment would affect study results"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators were blinded to allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "monthly discontinuation rates and reasons for withdrawal are comparable in both study arms"
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

van Wetering 2010

Methods	RCT; follow-up: 24 months, control group: usual care (pharmacotherapy according to guidelines, short smoking cessation advice by chest physician and recommendation to eat more in case of nutritional depletion)
Participants	Eligible: 199 Randomized: 199; I: 102, C: 97 Completed 4 months: I: 87; C: 88 Completed 24 months: I: 77; C: 81 Mean age I: 66 yrs, C: 67 yrs Sex: I: 71%; C: 71% Inclusion criteria: diagnosis of COPD according to guidelines, other inclusion criteria: impaired exercise capacity, W-max < 70%, GOLD 2+3 and clinical stable at inclusion. Major exclusion criteria: prior rehabilitation and patients with serious co-morbidity that precluded exercise therapy were excluded
Interventions	24-month program including: - Intensive 4-month standardized, supervised physiotherapy 2/week (30 min), with home-based exercises - Patients participated in an individualized education program - All smokers were offered smoking cessation counseling - Nutritionally depleted patients received counseling from a dietician - During the 20-month active maintenance phase, patients were instructed to train at home and visited the physiotherapist once a month. Dietician support was continued Included HCP: nurse, physiotherapist, dietician
Outcomes	SGRQ, total score and number of exacerbations, MRC dyspnoea scale, exercise performance (measured as maximum Watts: W-max), 6MWD, muscle strength, isometric quadriceps peak torque, maximal inspiratory mouth pressure, fat-free mass and lung function
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to INTERCOM or usual care using a computerised procedure with concealed patient allocation"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomised to INTERCOM or usual care using a computerised procedure with concealed patient allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation

van Wetering 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all outcome measurements were assessed single blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The results were analyzed by intention-to-treat
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Wakabayashi 2011

Methods	RCT; follow-up 12 months; control group: single intervention (education)
Participants	Eligible: 102 Randomized: 102; I: 52, C: 50 Completed: 85; I: 42, C: 43 Clinical diagnosis of COPD, > 65 years, exclusively visit the clinic with monthly scheduled appointments, have a history of cigarette smoking Exclusion criteria: history of atopy or any apparent asthmatic features, were illiterate or had cognitive impairment score of less than 26 on MMSE, lived in a residential care facility or a nursing home, had exacerbations during preceding 3 months, or had other respiratory diseases such as bronchiectasis, any type of pulmonary fibrosis or congestive heart failure
Interventions	Patients underwent a program of educational sessions for 6 months, individually tailored according to their domain scores on the LINQ questionnaire, which was designed to assess the need for information from a patients' perspective. The program was given by respiratory nurses and pulmonary physicians. There were six domains: 1) understanding of COPD, 2) pharmacological treatments, 3) exercise, 4) avoidance of exacerbations, including action plan with instructions in the event of exacerbations, 5) smoking cessation, 6) nutrition. All patients were provided with a booklet that was used during each session. After the intensive education period, each patient was followed up for 6 months in the same way as the patients in the usual care group Included HCP: nurse, pulmonologist
Outcomes	FEV1, MRC, SGRQ, 6MWD, Lung Information Needs Questionnaire (LINQ), BMI, BODE index (body mass index, dyspnoea, airflow obstruction, exercise capacity), Activities of Daily Living (ADL), co-morbidities, hospitalizations
Notes	Main component of program: self management/action plan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wakabayashi 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "a case manager independent of the study randomly assigned patients to either group I or group U using a computer-generated list"
Allocation concealment (selection bias)	Low risk	Quote: "Patients allocations were sealed in numbered envelopes by an independent evaluator, not involved in the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent evaluator, who assessed outcomes at the beginning of the study, after initial integrated education (6 months), and after follow-up period (6 months)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comparable drop-out rates between groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Wijkstra 1994

Methods	RCT; follow-up 12 weeks; control group: no treatment
Participants	Randomized: 45 Completed: 43 (I: 28; C: 15) Mean age I: 64 yrs, C: 62 yrs Sex (% male): I: 82%, C: 93% Inclusion criteria: diagnosis of COPD with FEV1 % < 60%, FEV1/IVC < 50% Exclusion criteria: evidence of ischaemic heart disease, intermittent claudication, musculoskeletal disorders or other disabling diseases that could restrict the rehab program
Interventions	Intervention program of 12 weeks: - Patients were supervised by a multidisciplinary team: pulmonologist, physiotherapist, nurse, GP - Patients visited physiotherapist twice a week for 12 weeks and the program consisted of conventional physiotherapy, upper limb training, inspiratory muscle training, exercise training. They had to practice twice a day for half an hour at home - Furthermore, they received education at home from a nurse (once a month) - They visited the GP once a month and he supervised clinical status and maintenance

Wijkstra 1994 (*Continued*)

	treatment Included HCP: GP, physiotherapist, nurse
Outcomes	Lung function, CRQ, cycle ergometer test
Notes	Main component of program: exercise

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were stratified for their FEV1 % predicted. After this stratification, the patients were randomly allocated"
Allocation concealment (selection bias)	Low risk	Quote: "(after randomisation), they were randomly allocated to one of three groups, each of 15 patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and treating therapists not likely to have been blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We could not ascertain how and whether outcome assessors were blinded to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 (out of 30) drop-outs in rehabilitation group versus no drop-outs in control group
Selective reporting (reporting bias)	Low risk	All outcomes reported

Wood-Baker 2006

Methods	Cluster-RCT; follow-up 12 months, control group: education + usual care
Participants	Eligible: 218 Randomized: 138; I: 67, C: 72 Completed (12 months): 112; I: 54, C: 58 Mean age I: 69 yrs, C: 71 yrs Sex (% male): I: 49%, C: 71% Inclusion criteria: COPD diagnosed by spirometry, age > 50 yrs, tobacco smoking history of greater than 10 pack-years and FEV1 < 65% predicted Exclusion criteria: nursing home residents

Wood-Baker 2006 (*Continued*)

Interventions	Control + intervention group: COPD information booklet, individual education session with nurse. Intervention group: written self management plan, which was developed in consultation with their treating GP. Patients were encouraged to make early contact with their GP during an exacerbation Included HCP: GP, nurse
Outcomes	SGRQ, exacerbations (courses of antibiotics/prednisone), ED and hospital admissions, GP consultations, spirometry, mortality, physical exercise (pedometer)
Notes	Prior to commencement of the randomisation process, only 50% of the included GPs attended one of a series of educational workshops on the management of COPD Main component of program: self management/action plan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Practices were randomised to the intervention or control group using a computer generated randomisation software package"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not likely that participants and personnel have been blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The baseline, 6- and 12-month assessments involved face to face contact with a research nurse at the GP's surgery or patients' home"
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 intervention patients versus 14 control patients missing at 6 months, reasons similar"
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Recruitment bias	Low risk	No information provided
Baseline imbalance between groups	High risk	Baseline imbalance between groups
Loss to follow-up of clusters	Low risk	No missing clusters

Adequate analysis methods for CRT	High risk	No adjusting for cluster-randomized trials

4MWT: four-minute walking test
6MWT/6MWD: six-minute walking test/six-minute walking distance
ADL: activities of daily living
BMI: body mass index
C: control
COOP: Dartmouth Primary Care Co-operative Quality of Life questionnaire
COPD: chronic obstructive pulmonary disease
CRQ: Chronic Respiratory Questionnaire
ED: emergency department
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
GP: general practitioner
HADS: Hospital Anxiety and Depression Scale
HCP: health care provider
HRQoL: health-related quality of life
I: intervention
MACL: Mood Adjective Check List
MCO: managed care organization
MMSE: Mini-Mental State Examination
MRC: Medical Research Council
PR: pulmonary rehabilitation
RCT: randomised controlled trial
SGRQ: St. George's Respiratory Questionnaire
SIP: Sickness Impact Profile
VAS: visual analogue scale
VC: vital capacity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aimonino 2008	Intervention duration less than 3 months
Bischoff 2012	No multidisciplinary intervention
Carrieri 2005	Active treatment in control group
Casas 2006	Intervention duration less than 3 months
De Godoy 2003	Active treatment in control group

(*Continued*)

Eaton 2009	Intervention duration less than 3 months
Effing 2009	Active treatment in control group
Efraimsson 2008	Fewer than 2 different health care providers included
Elliott 2004	Fewer than 2 different health care providers included
Garcia 2007	Duration of intervention less than 3 months
Gohl 2006	No multidisciplinary intervention and fewer than 2 components
Goldstein 1994	Fewer than 2 components of intervention
Guell 2008	Active treatment as control group
Hughes 2000	No results solely for COPD
Liu 2006	Not a RCT
Maltais 2008	No usual care as control group
Martin 2004	Fewer than 2 components of intervention
McGeoch 2006	Fewer than 2 components of intervention
Monninkhof 2003	No usual care as control group
Ries 2003	Active treatment as control group
Soler 2006	Active treatment as control group
Steele 2008	Active treatment as control group
Zhou 2010	COPD diagnosis was not inclusion criteria

COPD: chronic obstructive pulmonary disease
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Baumann 2012

Methods	Aim: to investigate whether relevant improvements in physical capabilities and quality of life in patients with chronic obstructive pulmonary disease (COPD) could be achieved by a long-term, low-intensity, once weekly rehabilitation program using limited resources. 100 patients with moderate to severe COPD were randomised to a continuous outpatient interdisciplinary rehabilitation program or standard care
Participants	100 patients with moderate to severe COPD
Interventions	Physiotherapy-led supervised outpatient training sessions were performed once weekly in addition to educational elements
Outcomes	Outcome measures at baseline and after 26 weeks were 6MWT, cycle ergometry and health-related quality of life
Notes	

Fan 2012

Methods	A randomised, controlled trial comparing CCMP with guideline-based usual care Setting: 20 Veterans Affairs hospital-based outpatient clinics
Participants	Patients hospitalised for COPD in the past year
Interventions	The CCMP included COPD education during 4 individual sessions and 1 group session, an action plan for identification and treatment of exacerbations, and scheduled proactive telephone calls for case management. Patients in both the intervention and usual care groups received a COPD informational booklet; their primary care providers received a copy of COPD guidelines and were advised to manage their patients according to these guidelines
Outcomes	The primary outcome was time to first COPD hospitalisation. Staff blinded to study group performed telephone-based assessment of COPD exacerbations and hospitalizations, and all hospitalizations were blindly adjudicated. Secondary outcomes included non-COPD health care use, all-cause mortality, health-related quality of life, patient satisfaction, disease knowledge and self efficacy
Notes	

Zwar 2012

Methods	Cluster-randomized controlled trial with blinded outcome assessment of 44 general practices in south-western Sydney comprising 451 people with a diagnosis of COPD, conducted between 2006 and 2009
Participants	COPD patients
Interventions	Participants from intervention group practices were visited at their home by a registered nurse with specific training in COPD care who worked with the general practitioner, the patient and other health professionals to develop and implement an individualized care plan based on best-practice guidelines. Participants from control group practices received usual care

Zwar 2012 (*Continued*)

Outcomes	The primary outcome was disease-related quality of life measured using the St George's Respiratory Questionnaire (SGRQ) at 12-month follow-up. Other outcomes were overall quality of life, lung function, smoking status, immunization status, patient knowledge of COPD and health service use
Notes	

CCMP: comprehensive care management program
COPD: chronic obstructive pulmonary disease

Characteristics of ongoing studies *[ordered by study ID]*

Bower 2012

Trial name or title	A cluster randomised controlled trial of the clinical and cost-effectiveness of a 'whole systems' model of self management support for the management of long-term conditions in primary care: trial protocol
Methods	The evaluation involves a large-scale, multi-site study of the implementation, effectiveness and cost-effectiveness of this model of self management support using a cluster-randomized controlled trial
Participants	Patients with 3 long-term conditions: diabetes, chronic obstructive pulmonary disease (COPD) and irritable bowel syndrome (IBS)
Interventions	The implementation and evaluation of self management support through an evidence-based 'whole systems' model involving patient support, training for primary care teams and service re-organization, all integrated into routine delivery within primary care
Outcomes	The outcome measures include healthcare utilization and quality of life
Starting date	
Contact information	TRIAL REGISTRATION NUMBER: ISRCTN: ISRCTN90940049
Notes	

Bunker 2012

Trial name or title	A pragmatic cluster randomised controlled trial of early intervention for chronic obstructive pulmonary disease by practice nurse-general practitioner teams
Methods	A pragmatic cluster-randomized trial will test the hypothesis that intervention by a practice nurse-general practitioner (GP) team leads to improved health-related quality of life and greater adherence with clinical practice guidelines for patients with newly diagnosed COPD, compared with usual care. 40 general practices in greater metropolitan Sydney Australia will be recruited to identify patients at risk of COPD and invite them to attend a case finding appointment. Practices will be randomised to deliver either practice nurse-GP partnership care, or usual care, to patients newly diagnosed with COPD

Bunker 2012 (*Continued*)

Participants	Patients with newly diagnosed COPD
Interventions	The active intervention will involve the practice nurse and GP working in partnership with the patient in developing and implementing a care plan involving (as appropriate), smoking cessation, immunization, pulmonary rehabilitation, medication review, assessment and correction of inhaler technique, nutritional advice, management of psycho-social issues, patient education and management of co-morbidities
Outcomes	The primary outcome measure is health-related quality of life, assessed with the St George's Respiratory Questionnaire 12 months after diagnosis. Secondary outcome measures include validated disease-specific and general health-related quality of life measures, smoking and immunization status, medications, inhaler technique and lung function. Outcomes will be assessed by project officers blinded to patients' randomisation groups
Starting date	
Contact information	TRIAL REGISTRATION: ACTRN12610000592044
Notes	

Byrnes 2012

Trial name or title	CAPICHe
Methods	Intention-to-treat study applying a prospective, randomised design comparing usual care with extensive outreach to encourage use of telephone health coaching for those people identified from a risk scoring algorithm as having a higher likelihood of future health costs
Participants	The trial population has been limited to people with one or more of the following selected chronic conditions: namely, low back pain, diabetes, coronary artery disease, heart failure and chronic obstructive pulmonary disease.This trial will enroll at least 64,835 sourced from the approximately 3 million Bupa Australia private health insured members located across Australia
Interventions	
Outcomes	The primary outcome will be the total (non-maternity) cost per member as reported to the private health insurer (i.e. charged to the insurer) 12 months following entry into the trial for each person
Starting date	Study recruitment will be completed in early 2012 and the results will be available in late 2013
Contact information	Australian New Zealand Clinical Trials Registry Reference: ACTRN12611000580976
Notes	

Freund 2011

Trial name or title	Primary care practice-based care management for chronically ill patients (PraCMan)
Methods	Cluster-randomized controlled trial with primary care practices as unit of randomisation. Patients are randomised in clusters of 15 to 20 patients per practice. Each patient is assigned to a care management team consisting of 1 primary care practice and 1 healthcare assistant
Participants	Primary care practices: participation of the practice in a centered care contract, at least 1 primary care practitioner, ability to perform on-site spirometry and home visits. Patients: suffering from type 2 diabetes mellitus, COPD, chronic heart failure or any combination, high risk for future hospitalisation, age 18 years or older. Major exclusions: active cancer disease, moderate to severe dementia, permanent residency in a nursing home, participation in a concurrent clinical trial, severe physical and mental disorders or other problems that hinder active participation in the intervention
Interventions	The intervention consists of 3 elements: 1) assessment of medical/non-medical needs and resources, including for example allergies, nutritional problems, depressions, falls, physical activity, smoking status. 2) planning and setting long-term goals for care management, 3) monitoring and structured follow-up. Prior to the intervention, all case management teams will be trained
Outcomes	Hospitalizations, mortality, EQ-5D, SF-12, PACIC, PHQ9, MARS, RAPA, smoking status, self management, pharmacy data, healthcare costs, ADL, comorbidity, home visits, COPD exacerbations, BMI, dyspnoea, FEV
Starting date	July 2010
Contact information	tobias.freund@med.uni-heidelberg.de
Notes	ISRCTN56104508

Gomez 2006

Trial name or title	Efficacy of respiratory rehabilitation on patients with moderate COPD in primary care and maintenance of benefits at 2 years
Methods	RCT; 3 groups in parallel with blind evaluation. Control group: customary care. 56 patients per group are needed
Participants	Patients with a diagnosis of moderate COPD according to GOLD
Interventions	3 groups: 1) pulmonary rehabilitation (educational sessions, respiratory physiotherapy, low-intensity physical exercise) for 12 weeks and program maintenance for 24 months; 2) pulmonary rehabilitation for 12 weeks without maintenance program, 3) control group
Outcomes	Quality of life with Chronic Respiratory Questionnaire, 6MWD, Borg dyspnoea Scale, MRC Dyspnea Score, lung function
Starting date	Finished, results not yet published
Contact information	

Gomez 2006 (*Continued*)

Notes	

Jones 2009a

Trial name or title	Effect of a case management study on primary care use and prescribing for AECOPD
Methods	RCT
Participants	Patients admitted to hospital with an exacerbation of COPD
Interventions	Intensive case management (including hospital and home visits), exercise, education and access to support 7 days a week (phone line) and nurse/doctor review 5 days a week. Control group: usual care
Outcomes	Data on all GP and practice nurse visits to either surgery or home and prescriptions for antibiotics and steroids (including all primary and secondary care prescriptions) were collected during the 12-month study period
Starting date	
Contact information	
Notes	Results submitted, not accepted yet

Kruis 2013

Trial name or title	RECODE
Methods	RECODE is a cluster-randomized trial with 2 years of follow-up, during which 40 clusters of primary care teams (including 1086 COPD patients) are randomised to IDM or usual care
Participants	COPD patients
Interventions	The intervention started with a 2-day multidisciplinary course in which health care providers are trained as a team in essential components of effective COPD IDM in primary care. During the course, the team redesigns the care process and defines responsibilities of different caregivers. They are trained in how to use feedback on process and outcome data to guide implement guideline-driven integrated healthcare. Practice-tailored feedback reports are provided at baseline, and at 6 and 12 months. The team learns the details of an ICT program that supports recording of process and outcome measures. Afterwards, the team designs a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. After 6 and 12 months, there is a refresher course for all teams simultaneously to enable them to learn from each other's experience
Outcomes	Health status of patients at 12 months is the primary outcome, measured by the Clinical COPD Questionnaire (CCQ) Secondary outcomes include effects on quality of care, disease-specific and generic health-related quality of life, COPD exacerbations, dyspnoea, costs of healthcare utilization and productivity loss
Starting date	1 September 2010

Contact information	a.l.kruis@lumc.nl; Netherlands Trial Register (NTR): NTR2268
Notes	

Murphy 2011

Trial name or title	The effectiveness of a structured education pulmonary rehabilitation programme for improving the health status of people with Chronic Obstructive Pulmonary Disease (COPD): The PRINCE study
Methods	This study evaluated the effectiveness of a structured education pulmonary rehabilitation program (SEPRP), delivered at the level of the general practice, on the health status of people with COPD. A cluster-randomized controlled trial was employed with the General Practice as the unit of randomisation
Participants	All adults with a diagnosis of COPD were eligible to participate
Interventions	The experimental group received a SEPRP, designed in consultation with people with COPD, experts, general practitioners and practice nurses. It was delivered 2 hours per week over 8 weeks by practice nurses and physiotherapists. The control group received 'usual care'
Outcomes	The primary outcome measure was health status measured by the Chronic Respiratory Questionnaire (CRQ) at 12 to 14 weeks
Starting date	
Contact information	
Notes	

Roman 2013

Trial name or title	Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomised controlled trial
Methods	This study aimed to assess the efficacy of a 3-month Pulmonary Rehabilitation (PR) program with a further 9 months of maintenance (RHBM group) compared with both PR for 3 months without further maintenance (RHB group) and usual care in improving the quality of life of patients with moderate COPD. The authors conducted a parallel-group, randomised clinical trial in Majorca primary health care in which 97 patients with moderate COPD were assigned to the 3 groups
Participants	Moderate COPD
Interventions	See above
Outcomes	Health outcomes were quality of life, exercise capacity, pulmonary function and exacerbations
Starting date	

Contact information	ISRCTN94514482
Notes	

6MWD: six-minute walking distance
ADL: activities of daily living
BMI: body mass index
COPD: chronic obstructive pulmonary disease
FEV: forced expiratory volume
GOLD: Global Initiative for Chronic Obstructive Lung Disease
IDM: integrated disease management
MRC: Medical Research Council
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Integrated disease management versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SGRQ: short-term (3 to 12 months)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 SGRQ: Total	13	1425	Mean Difference (IV, Random, 95% CI)	-3.71 [-5.83, -1.59]
1.2 SGRQ: Symptoms	11	1377	Mean Difference (IV, Random, 95% CI)	-2.39 [-5.31, 0.53]
1.3 SGRQ: Activity	11	1352	Mean Difference (IV, Random, 95% CI)	-2.70 [-4.84, -0.55]
1.4 SGRQ: Impact	11	1355	Mean Difference (IV, Random, 95% CI)	-4.04 [-5.96, -2.11]
2 SGRQ: long-term (> 12 months)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 SGRQ: Total	2	189	Mean Difference (IV, Random, 95% CI)	-0.22 [-7.43, 6.99]
2.2 SGRQ: Symptoms	2	191	Mean Difference (IV, Random, 95% CI)	5.65 [-8.88, 20.18]
2.3 SGRQ: Activity	2	191	Mean Difference (IV, Random, 95% CI)	-2.13 [-7.89, 3.63]
2.4 SGRQ: Impact	2	182	Mean Difference (IV, Random, 95% CI)	-1.62 [-5.50, 2.25]
3 Subgroup analysis SGRQ (total score) based on type of setting	13	1425	Mean Difference (IV, Random, 95% CI)	-3.77 [-5.90, -1.64]
3.1 Primary care	6	456	Mean Difference (IV, Random, 95% CI)	-4.68 [-8.80, -0.56]
3.2 Secondary care	7	969	Mean Difference (IV, Random, 95% CI)	-3.41 [-5.97, -0.85]
4 Subgroup analysis SGRQ (total score) based on type of study design	13	1425	Mean Difference (IV, Random, 95% CI)	-3.71 [-5.83, -1.59]
4.1 RCTs	12	1304	Mean Difference (IV, Random, 95% CI)	-4.22 [-6.14, -2.30]
4.2 CRCTs	1	121	Mean Difference (IV, Random, 95% CI)	2.3 [-1.62, 6.22]
5 Subgroup analysis SGRQ (total score) based on type of control group	13	1425	Mean Difference (IV, Random, 95% CI)	-3.71 [-5.83, -1.59]
5.1 Control group: usual care	9	744	Mean Difference (IV, Random, 95% CI)	-4.09 [-6.35, -1.84]
5.2 Control group: mono-disciplinary treatment	4	681	Mean Difference (IV, Random, 95% CI)	-2.98 [-7.69, 1.74]
6 Subgroup analysis SGRQ (total score) based on dominant component of intervention	11	1315	Mean Difference (IV, Random, 95% CI)	-3.61 [-5.67, -1.55]
6.1 Dominant component self management	5	942	Mean Difference (IV, Random, 95% CI)	-2.76 [-5.88, 0.36]
6.2 Dominant component exercise	6	373	Mean Difference (IV, Random, 95% CI)	-4.74 [-7.05, -2.43]
7 CRQ: short-term (3 to 12 months)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 CRQ: Dyspnea	4	160	Mean Difference (IV, Random, 95% CI)	1.02 [0.67, 1.36]
7.2 CRQ: Fatigue	4	161	Mean Difference (IV, Random, 95% CI)	0.82 [0.46, 1.17]
7.3 CRQ: Emotion	4	161	Mean Difference (IV, Random, 95% CI)	0.61 [0.26, 0.95]
7.4 CRQ: Mastery	4	161	Mean Difference (IV, Random, 95% CI)	0.75 [0.38, 1.12]
8 CRQ: Long-term (> 12 months)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 CRQ: Dyspnea	2	151	Mean Difference (IV, Random, 95% CI)	0.47 [-0.31, 1.25]
8.2 CRQ: Fatigue	2	151	Mean Difference (IV, Random, 95% CI)	0.45 [0.05, 0.85]
8.3 CRQ: Emotion	2	151	Mean Difference (IV, Random, 95% CI)	0.53 [0.10, 0.95]

8.4 CRQ: Mastery	2	151	Mean Difference (IV, Random, 95% CI)	0.80 [0.37, 1.23]
9 General health QoL: SIP mean difference	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 SIP total	2	183	Mean Difference (IV, Random, 95% CI)	-1.06 [-3.00, 0.89]
9.2 SIP: physical	2	183	Mean Difference (IV, Random, 95% CI)	-2.63 [-5.55, 0.30]
9.3 SIP: psychosocial	2	183	Mean Difference (IV, Random, 95% CI)	-0.86 [-3.17, 1.44]
10 Functional exercise capacity: 6MWD mean difference	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 6MWD: short-term (3 to 12 months)	14	871	Mean Difference (IV, Random, 95% CI)	43.86 [21.83, 65.89]
10.2 6MWD: long-term (> 12 months)	2	184	Mean Difference (IV, Random, 95% CI)	16.84 [3.01, 30.67]
11 Subgroup analysis 6MWD based on type of setting	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Primary care	7	427	Mean Difference (IV, Random, 95% CI)	45.16 [8.65, 81.67]
11.2 Secondary care	7	438	Mean Difference (IV, Random, 95% CI)	49.18 [14.28, 84.08]
11.3 Tertiary care	1	35	Mean Difference (IV, Random, 95% CI)	85.0 [30.43, 139.57]
12 Subgroup analysis 6MWD based on type of control group	14	871	Mean Difference (IV, Random, 95% CI)	43.86 [21.83, 65.89]
12.1 Control group: mono disciplinary treatment	4	180	Mean Difference (IV, Random, 95% CI)	35.99 [-5.34, 77.31]
12.2 Control group: usual care	10	691	Mean Difference (IV, Random, 95% CI)	46.59 [19.68, 73.51]
13 Subgroup analysis 6MWD based on dominant component of intervention	14	871	Mean Difference (IV, Random, 95% CI)	43.86 [21.83, 65.89]
13.1 Dominant component: exercise	12	653	Mean Difference (IV, Random, 95% CI)	51.47 [26.53, 76.40]
13.2 Dominant component: structured follow-up	1	133	Mean Difference (IV, Random, 95% CI)	3.50 [-28.31, 35.31]
13.3 Dominant component: individually tailored education program	1	85	Mean Difference (IV, Random, 95% CI)	0.4 [-39.64, 40.44]
14 Maximal exercise capacity: cycle test (W-max)	4	298	Mean Difference (IV, Random, 95% CI)	6.99 [2.96, 11.02]
15 Number of patients experiencing at least one exacerbation: short-term (3-12 months)	2	407	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.77, 1.91]
16 Number of patients experiencing at least one exacerbation: long-term (> 12 months)	2	301	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.90, 2.60]
17 All hospital admissions: short-term (3 to 12 months)	2	266	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.36, 1.07]
18 All hospital admissions: long-term (> 12 months)	2	283	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.38, 1.57]
19 Respiratory-related hospital admissions: short-term (3 to 12 months)	7	1470	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.99]

20 Respiratory-related hospital admissions: long-term (> 12 months)	1	179	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.28, 1.22]
21 Hospital days per patient (all causes): short-term (3 to 12 months)	6	741	Mean Difference (IV, Random, 95% CI)	-3.78 [-5.90, -1.67]
22 Hospital days per patient: long-term (> 12 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23 ED visits	4	1161	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.33, 1.25]
24 Number of patients using at least one course of oral steroids	3	348	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.64, 2.01]
25 Number of patients using at least one course of antibiotics	2	236	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.24, 8.48]
26 MRC dyspnea score	3	345	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.48, -0.11]
27 Borg score	3	145	Mean Difference (IV, Random, 95% CI)	0.14 [-0.70, 0.98]
28 Mortality	5	1235	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.49, 1.46]
28.1 Short-term (3 to 12 months)	4	1113	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.52, 1.74]
28.2 Long-term (> 12 months)	1	122	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.28]
29 FEV1 (liter)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 FEV1 (liter): short-term	2	234	Mean Difference (IV, Random, 95% CI)	0.00 [-0.14, 0.14]
29.2 FEV1 (liter): long-term	1	104	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.28, 0.06]
30 FEV1 (% predicted)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
30.1 FEV1 (% predicted): short-term	4	280	Mean Difference (IV, Random, 95% CI)	-0.57 [-3.54, 2.39]
30.2 FEV1 (% predicted; mean change): short-term	4	514	Mean Difference (IV, Random, 95% CI)	2.15 [0.38, 3.91]
30.3 FEV1 (% predicted): long-term	1	104	Mean Difference (IV, Random, 95% CI)	-4.60 [-11.26, 2.06]
31 Anxiety and depression (HADS)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
31.1 HADS: depression	2	316	Mean Difference (IV, Random, 95% CI)	0.21 [-0.39, 0.81]
31.2 HADS: anxiety	2	316	Mean Difference (IV, Random, 95% CI)	0.22 [-0.41, 0.85]

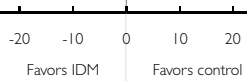
Analysis 1.1. Comparison 1 Integrated disease management versus control, Outcome 1 SGRQ: short-term (3 to 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 1 SGRQ: short-term (3 to 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SGRQ: Total							
Bourbeau 2003	88	-6.4 (11.8)	84	-2.3 (11.5)		11.6 %	-4.10 [-7.58, -0.62]
Boxall 2005	23	-5.8 (11.8)	23	-1.4 (13.3)		5.6 %	-4.40 [-11.67, 2.87]
Dheda 2004	10	-21 (20.4)	15	-0.2 (12.6)		2.0 %	-20.80 [-34.96, -6.64]
Engstrom 1999	26	0.3 (17.3)	24	0.5 (16.8)		3.9 %	-0.20 [-9.65, 9.25]
Fernandez 2009	27	-14.7 (13.8)	14	-2.5 (12.7)		4.6 %	-12.20 [-20.65, -3.75]
Gottlieb 2011	17	-5.2 (14.2)	18	0.42 (11.3)		4.5 %	-5.62 [-14.15, 2.91]
Koff 2009	19	-10.3 (14.7)	19	-0.6 (12.2)		4.5 %	-9.70 [-18.29, -1.11]
Rice 2010	225	1.3 (13.21)	209	6.24 (13.44)		13.6 %	-4.94 [-7.45, -2.43]
Theander 2009	12	-7.6 (10.8)	14	-2.6 (12.2)		4.3 %	-5.00 [-13.84, 3.84]
Trappenburg 2011	82	0.4 (11.5)	95	1.2 (10.5)		12.0 %	-0.80 [-4.06, 2.46]
van Wetering 2010	87	-3.9 (10.3)	88	0.3 (9.4)		12.7 %	-4.20 [-7.12, -1.28]
Wakabayashi 2011	42	-2.07 (9.46)	43	-1.57 (10.3)		10.1 %	-0.50 [-4.70, 3.70]
Wood-Baker 2006	60	-1.1 (11.2)	61	-3.4 (10.8)		10.7 %	2.30 [-1.62, 6.22]
Subtotal (95% CI)	**718**		**707**			**100.0 %**	**-3.71 [-5.83, -1.59]**
Heterogeneity: Tau^2 = 6.97; Chi^2 = 27.19, df = 12 (P = 0.01); I^2 =56%							
Test for overall effect: Z = 3.43 (P = 0.00061)							
2 SGRQ: Symptoms							
Bourbeau 2003	88	-1.5 (19.4)	84	-1.1 (15.7)		15.2 %	-0.40 [-5.66, 4.86]
Boxall 2005	23	2 (18.9)	23	-0.6 (19.3)		5.7 %	2.60 [-8.44, 13.64]
Engstrom 1999	26	-7.5 (23.5)	24	-4.1 (23)		4.4 %	-3.40 [-16.29, 9.49]
Fernandez 2009	27	-22.8 (20.4)	14	-9.1 (17.3)		5.0 %	-13.70 [-25.59, -1.81]
Gottlieb 2011	21	-3.14 (20.7)	20	-3.63 (18.6)		4.9 %	0.49 [-11.54, 12.52]
Koff 2009	19	-12.8 (24.1)	19	-3.3 (22.2)		3.5 %	-9.50 [-24.23, 5.23]
Rice 2010	252	-0.26 (20.42)	234	5.38 (20.92)		20.3 %	-5.64 [-9.32, -1.96]
Theander 2009	12	-10.6 (22.3)	14	0.5 (29.3)		2.0 %	-11.10 [-30.97, 8.77]



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Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Trappenburg 2011	84	-3.6 (21.1)	97	-0.6 (20.3)		13.1 %	-3.00 [-9.06, 3.06]
van Wetering 2010	87	-3 (17.7)	88	-1.4 (16.9)		15.5 %	-1.60 [-6.73, 3.53]
Wood-Baker 2006	60	-2.5 (20.8)	61	-8.9 (19.9)		10.5 %	6.40 [-0.86, 13.66]
Subtotal (95% CI)	**699**		**678**			**100.0 %**	**-2.39 [-5.31, 0.53]**
Heterogeneity: Tau^2 = 7.44; Chi^2 = 15.38, df = 10 (P = 0.12); I^2 =35%							
Test for overall effect: Z = 1.60 (P = 0.11)							
3 SGRQ: Activity							
Bourbeau 2003	88	-4.5 (15.1)	84	-1.8 (14.7)		13.8 %	-2.70 [-7.15, 1.75]
Boxall 2005	23	-5.9 (12.8)	23	-1 (15.4)		5.7 %	-4.90 [-13.08, 3.28]
Engstrom 1999	26	0.7 (17.8)	24	-0.4 (14.2)		5.0 %	1.10 [-7.79, 9.99]
Fernandez 2009	27	-11.2 (13.9)	14	0 (12.1)		5.7 %	-11.20 [-19.43, -2.97]
Gottlieb 2011	18	1.29 (24)	19	-2.22 (23.2)		1.9 %	3.51 [-11.71, 18.73]
Koff 2009	19	-8.8 (20.7)	19	-0.5 (17.4)		2.8 %	-8.30 [-20.46, 3.86]
Rice 2010	240	1.47 (14.03)	226	5.37 (14.13)		22.9 %	-3.90 [-6.46, -1.34]
Theander 2009	12	-2.5 (13.1)	14	-2.7 (14)		3.8 %	0.20 [-10.23, 10.63]
Trappenburg 2011	84	2.7 (16.4)	96	2.8 (17.1)		12.2 %	-0.10 [-5.00, 4.80]
van Wetering 2010	87	-3.9 (14)	88	0.9 (13.1)		15.5 %	-4.80 [-8.82, -0.78]
Wood-Baker 2006	60	2.5 (15.5)	61	-0.7 (14.7)		10.8 %	3.20 [-2.18, 8.58]
Subtotal (95% CI)	**684**		**668**			**100.0 %**	**-2.70 [-4.84, -0.55]**
Heterogeneity: Tau^2 = 3.51; Chi^2 = 14.33, df = 10 (P = 0.16); I^2 =30%							
Test for overall effect: Z = 2.47 (P = 0.014)							
4 SGRQ: Impact							
Bourbeau 2003	88	-9.1 (13.7)	84	-2.9 (15.7)		12.4 %	-6.20 [-10.61, -1.79]
Boxall 2005	23	-8.1 (17.1)	23	-2 (17.6)		3.3 %	-6.10 [-16.13, 3.93]
Engstrom 1999	26	2.6 (19.4)	24	2.5 (20.1)		2.8 %	0.10 [-10.87, 11.07]
Fernandez 2009	27	-14.3 (16.3)	14	-1.8 (16.9)		2.9 %	-12.50 [-23.28, -1.72]
Gottlieb 2011	18	-4.77 (12.8)	20	-0.08 (8.7)		6.2 %	-4.69 [-11.73, 2.35]
Koff 2009	19	-6.6 (18.1)	19	-0.6 (13.7)		3.2 %	-6.00 [-16.21, 4.21]
Rice 2010	246	1.61 (16.16)	223	7.66 (16.63)		19.3 %	-6.05 [-9.02, -3.08]
Theander 2009	12	-9.7 (15.5)	14	-3.4 (10.7)		3.1 %	-6.30 [-16.71, 4.11]
Trappenburg 2011	84	-0.01 (12.3)	95	0.8 (9.8)		17.6 %	-0.81 [-4.10, 2.48]
van Wetering 2010	87	-4.1 (11.2)	88	0.5 (12.2)		16.6 %	-4.60 [-8.07, -1.13]
Wood-Baker 2006	60	-2.7 (13.1)	61	-3.2 (11.7)		12.4 %	0.50 [-3.93, 4.93]

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Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**690**		**665**			**100.0 %**	**-4.04 [-5.96, -2.11]**

Heterogeneity: Tau² = 2.69; Chi² = 13.95, df = 10 (P = 0.18); I² =28%

Test for overall effect: Z = 4.11 (P = 0.000040)

-20 -10 0 10 20

Favors IDM Favors control

Analysis 1.2. Comparison 1 Integrated disease management versus control, Outcome 2 SGRQ: long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 2 SGRQ: long-term (> 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SGRQ: Total							
Gottlieb 2011	15	-0.47 (17.8)	17	-5.93 (11)		29.5 %	5.46 [-4.96, 15.88]
van Wetering 2010	77	-1.37 (8.073)	80	1.23 (8.0498)		70.5 %	-2.60 [-5.12, -0.08]
Subtotal (95% CI)	**92**		**97**			**100.0 %**	**-0.22 [-7.43, 6.99]**

Heterogeneity: Tau² = 17.53; Chi² = 2.17, df = 1 (P = 0.14); I² =54%

Test for overall effect: Z = 0.06 (P = 0.95)

2 SGRQ: Symptoms							
Gottlieb 2011	16	3.92 (18.5)	18	-10.58 (19.9)		41.2 %	14.50 [1.59, 27.41]
van Wetering 2010	77	-1.5 (12.1095)	80	-0.94 (11.8959)		58.8 %	-0.56 [-4.32, 3.20]
Subtotal (95% CI)	**93**		**98**			**100.0 %**	**5.65 [-8.88, 20.18]**

Heterogeneity: Tau² = 89.87; Chi² = 4.82, df = 1 (P = 0.03); I² =79%

Test for overall effect: Z = 0.76 (P = 0.45)

3 SGRQ: Activity							
Gottlieb 2011	16	-0.61 (28.4)	18	-7.22 (22.6)		10.2 %	6.61 [-10.79, 24.01]
van Wetering 2010	77	-1.29 (11.4952)	80	1.83 (11.4487)		89.8 %	-3.12 [-6.71, 0.47]

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Favors IDM Favors control

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Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**93**		**98**			**100.0 %**	**-2.13 [-7.89, 3.63]**
Heterogeneity: Tau^2 = 6.27; Chi^2 = 1.15, df = 1 (P = 0.28); I^2 =13%							
Test for overall effect: Z = 0.72 (P = 0.47)							
4 SGRQ: Impact							
Gottlieb 2011	15	-0.74 (14.3)	17	-3 (6.4)		20.6 %	2.26 [-5.59, 10.11]
van Wetering 2010	70	-1.34 (8.3666)	80	1.29 (8.7654)		79.4 %	-2.63 [-5.37, 0.11]
Subtotal (95% CI)	**85**		**97**			**100.0 %**	**-1.62 [-5.50, 2.25]**
Heterogeneity: Tau^2 = 2.95; Chi^2 = 1.33, df = 1 (P = 0.25); I^2 =25%							
Test for overall effect: Z = 0.82 (P = 0.41)							

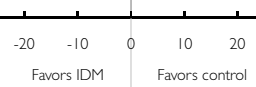
Analysis 1.3. Comparison 1 Integrated disease management versus control, Outcome 3 Subgroup analysis SGRQ (total score) based on type of setting.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 3 Subgroup analysis SGRQ (total score) based on type of setting

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Primary care							
Boxall 2005	23	-5.8 (11.8)	23	-1.4 (13.3)		5.7 %	-4.40 [-11.67, 2.87]
Fernandez 2009	27	-14.7 (13.8)	14	-2.5 (12.7)		4.6 %	-12.20 [-20.65, -3.75]
Gottlieb 2011	17	-5.2 (14.2)	18	0.42 (11.3)		4.6 %	-5.62 [-14.15, 2.91]
Koff 2009	19	-10.3 (14.7)	19	-0.6 (12.2)		4.5 %	-9.70 [-18.29, -1.11]
van Wetering 2010	87	-3.9 (10.3)	88	0.3 (9.4)		13.0 %	-4.20 [-7.12, -1.28]
Wood-Baker 2006	60	-1.1 (11.2)	61	-3.4 (10.8)		10.9 %	2.30 [-1.62, 6.22]
Subtotal (95% CI)	**233**		**223**			**43.3 %**	**-4.68 [-8.80, -0.56]**
Heterogeneity: Tau^2 = 15.77; Chi^2 = 14.97, df = 5 (P = 0.01); I^2 =67%							
Test for overall effect: Z = 2.23 (P = 0.026)							
2 Secondary care							
Bourbeau 2003	88	-6.4 (11.8)	84	-2.3 (11.5)		11.8 %	-4.10 [-7.58, -0.62]
Dheda 2004	10	-21 (20.4)	15	-0.2 (12.6)		2.0 %	-20.80 [-34.96, -6.64]
Engstrom 1999	26	0.3 (17.3)	24	0.5 (16.8)		3.9 %	-0.20 [-9.65, 9.25]
Rice 2010	225	1.3 (13.21)	209	6.24 (13.44)		13.9 %	-4.94 [-7.45, -2.43]
Theander 2009	12	-7.6 (10.8)	14	-2.6 (12.2)		4.3 %	-5.00 [-13.84, 3.84]
Trappenburg 2011	82	0.4 (11.5)	95	1.2 (10.5)		12.2 %	-0.80 [-4.06, 2.46]
Wakabayashi 2011	42	-2.2 (12.2)	43	-1.6 (12.3)		8.5 %	-0.60 [-5.81, 4.61]
Subtotal (95% CI)	**485**		**484**			**56.7 %**	**-3.41 [-5.97, -0.85]**
Heterogeneity: Tau^2 = 4.86; Chi^2 = 11.51, df = 6 (P = 0.07); I^2 =48%							
Test for overall effect: Z = 2.61 (P = 0.0091)							
Total (95% CI)	**718**		**707**			**100.0 %**	**-3.77 [-5.90, -1.64]**
Heterogeneity: Tau^2 = 6.88; Chi^2 = 26.49, df = 12 (P = 0.01); I^2 =55%							
Test for overall effect: Z = 3.47 (P = 0.00053)							
Test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.61), I^2 =0.0%							

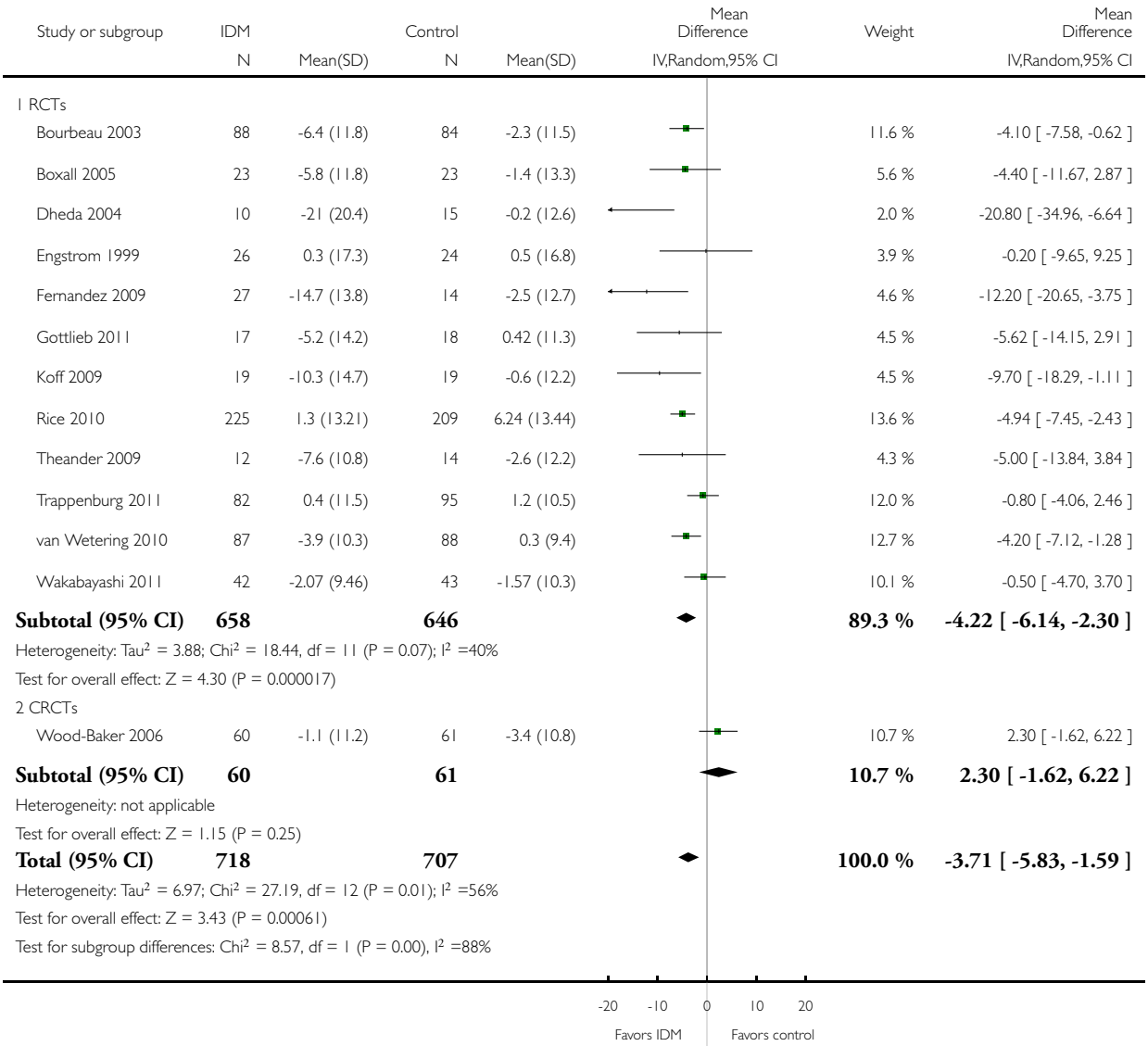


Analysis 1.4. Comparison 1 Integrated disease management versus control, Outcome 4 Subgroup analysis SGRQ (total score) based on type of study design.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 4 Subgroup analysis SGRQ (total score) based on type of study design

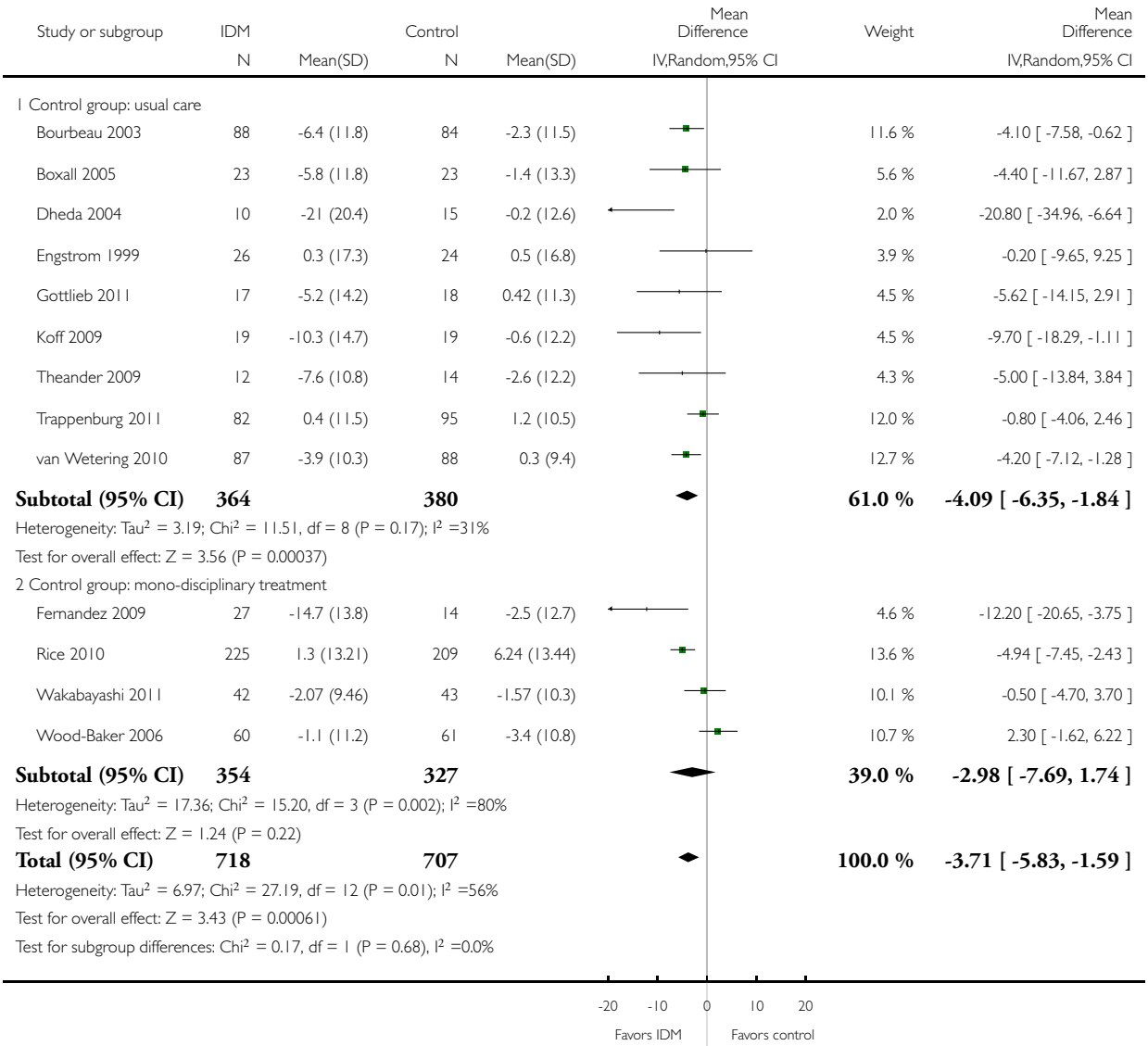


Analysis 1.5. Comparison 1 Integrated disease management versus control, Outcome 5 Subgroup analysis SGRQ (total score) based on type of control group.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 5 Subgroup analysis SGRQ (total score) based on type of control group



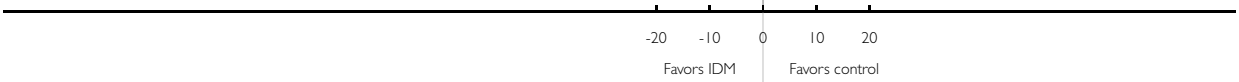
Analysis 1.6. Comparison 1 Integrated disease management versus control, Outcome 6 Subgroup analysis SGRQ (total score) based on dominant component of intervention.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 6 Subgroup analysis SGRQ (total score) based on dominant component of intervention

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Dominant component self management							
Bourbeau 2003	88	-6.4 (11.8)	84	-2.3 (11.5)		13.6 %	-4.10 [-7.58, -0.62]
Koff 2009	19	-10.3 (14.7)	19	-0.6 (12.2)		4.6 %	-9.70 [-18.29, -1.11]
Rice 2010	225	1.3 (13.21)	209	6.24 (13.44)		16.7 %	-4.94 [-7.45, -2.43]
Trappenburg 2011	82	0.4 (11.5)	95	1.2 (10.5)		14.2 %	-0.80 [-4.06, 2.46]
Wood-Baker 2006	60	-1.1 (11.2)	61	-3.4 (10.8)		12.3 %	2.30 [-1.62, 6.22]
Subtotal (95% CI)	**474**		**468**			**61.3 %**	**-2.76 [-5.88, 0.36]**
Heterogeneity: Tau^2 = 8.33; Chi^2 = 13.74, df = 4 (P = 0.01); I^2 =71%							
Test for overall effect: Z = 1.73 (P = 0.083)							
2 Dominant component exercise							
Boxall 2005	23	-5.8 (11.8)	23	-1.4 (13.3)		5.9 %	-4.40 [-11.67, 2.87]
Engstrom 1999	26	0.3 (17.3)	24	0.5 (16.8)		3.9 %	-0.20 [-9.65, 9.25]
Fernandez 2009	27	-14.7 (13.8)	14	-2.5 (12.7)		4.7 %	-12.20 [-20.65, -3.75]
Gottlieb 2011	17	-5.2 (14.2)	18	0.42 (11.3)		4.6 %	-5.62 [-14.15, 2.91]
Theander 2009	12	-7.6 (10.8)	14	-2.6 (12.2)		4.3 %	-5.00 [-13.84, 3.84]
van Wetering 2010	87	-3.9 (10.3)	88	0.3 (9.4)		15.3 %	-4.20 [-7.12, -1.28]
Subtotal (95% CI)	**192**		**181**			**38.7 %**	**-4.74 [-7.05, -2.43]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.07, df = 5 (P = 0.54); I^2 =0.0%							
Test for overall effect: Z = 4.02 (P = 0.000057)							
Total (95% CI)	**666**		**649**			**100.0 %**	**-3.61 [-5.67, -1.55]**
Heterogeneity: Tau^2 = 4.97; Chi^2 = 19.57, df = 10 (P = 0.03); I^2 =49%							
Test for overall effect: Z = 3.44 (P = 0.00058)							
Test for subgroup differences: Chi^2 = 1.00, df = 1 (P = 0.32), I^2 =0.0%							



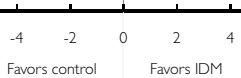
Analysis 1.7. Comparison 1 Integrated disease management versus control, Outcome 7 CRQ: short-term (3 to 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 7 CRQ: short-term (3 to 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 CRQ: Dyspnea							
Cambach 1997	14	1.2 (1.2)	8	0 (0.8)		17.2 %	1.20 [0.36, 2.04]
Güell 2000	30	0.98 (1.1338)	30	-0.03 (0.9695)		42.4 %	1.01 [0.47, 1.54]
Güell 2006	18	0.8 (1.2)	17	-0.2 (1.2)		19.1 %	1.00 [0.20, 1.80]
Wijkstra 1994	28	0.86 (1)	15	-0.04 (1.3)		21.2 %	0.90 [0.15, 1.65]
Subtotal (95% CI)	**90**		**70**			**100.0 %**	**1.02 [0.67, 1.36]**
Heterogeneity: Tau² = 0.0; Chi² = 0.28, df = 3 (P = 0.96); I² =0.0%							
Test for overall effect: Z = 5.73 (P < 0.00001)							
2 CRQ: Fatigue							
Cambach 1997	15	1.25 (1)	8	0 (1)		17.2 %	1.25 [0.39, 2.11]
Güell 2000	30	0.75 (0.9969)	30	-0.05 (1.2433)		39.0 %	0.80 [0.23, 1.37]
Güell 2006	18	0.2 (1.1)	17	-0.5 (1.3)		19.8 %	0.70 [-0.10, 1.50]
Wijkstra 1994	28	0.88 (1.3)	15	0.25 (1.08)		23.9 %	0.63 [-0.10, 1.36]
Subtotal (95% CI)	**91**		**70**			**100.0 %**	**0.82 [0.46, 1.17]**
Heterogeneity: Tau² = 0.0; Chi² = 1.32, df = 3 (P = 0.73); I² =0.0%							
Test for overall effect: Z = 4.50 (P < 0.00001)							
3 CRQ: Emotion							
Cambach 1997	15	0.71 (1.14)	8	0.29 (1)		14.6 %	0.42 [-0.48, 1.32]
Güell 2000	30	0.819 (1.2871)	30	0.11 (1.1886)		30.1 %	0.71 [0.09, 1.34]
Güell 2006	18	0.3 (1)	17	-0.4 (1.2)		22.0 %	0.70 [-0.03, 1.43]
Wijkstra 1994	28	0.56 (0.99)	15	0.03 (0.93)		33.3 %	0.53 [-0.07, 1.13]
Subtotal (95% CI)	**91**		**70**			**100.0 %**	**0.61 [0.26, 0.95]**
Heterogeneity: Tau² = 0.0; Chi² = 0.40, df = 3 (P = 0.94); I² =0.0%							
Test for overall effect: Z = 3.46 (P = 0.00055)							
4 CRQ: Mastery							
Cambach 1997	15	1 (1.25)	8	-0.25 (1)		15.8 %	1.25 [0.31, 2.19]
Güell 2000	30	0.917 (1.2324)	30	0.15 (1.5062)		28.6 %	0.77 [0.07, 1.46]
Güell 2006	18	0.6 (1.1)	17	0 (1.1)		26.1 %	0.60 [-0.13, 1.33]



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Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Wijkstra 1994	28	0.6 (1.2)	15	0 (1.03)		29.6 %	0.60 [-0.09, 1.29]
Subtotal (95% CI)	**91**		**70**			**100.0 %**	**0.75 [0.38, 1.12]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.44$, df = 3 (P = 0.70); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.95 (P = 0.000079)							

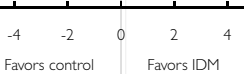
Analysis 1.8. Comparison 1 Integrated disease management versus control, Outcome 8 CRQ: Long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 8 CRQ: Long-term (> 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 CRQ: Dyspnea							
Güell 2000	24	1.029 (1.4011)	23	0.11 (1.1414)		43.6 %	0.92 [0.19, 1.65]
Sridhar 2008	55	-0.72 (1.2)	49	-0.84 (1.2)		56.4 %	0.12 [-0.34, 0.58]
Subtotal (95% CI)	**79**		**72**			**100.0 %**	**0.47 [-0.31, 1.25]**
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 3.32$, df = 1 (P = 0.07); $I^2 = 70\%$							
Test for overall effect: Z = 1.18 (P = 0.24)							
2 CRQ: Fatigue							
Güell 2000	24	0.231 (1.1562)	23	-0.32 (1.4387)		28.6 %	0.55 [-0.19, 1.30]
Sridhar 2008	55	0.06 (1.35)	49	-0.35 (1.11)		71.4 %	0.41 [-0.06, 0.88]
Subtotal (95% CI)	**79**		**72**			**100.0 %**	**0.45 [0.05, 0.85]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.21 (P = 0.027)							
3 CRQ: Emotion							
Güell 2000	24	0.651 (1.1856)	23	0.12 (1.3572)		34.1 %	0.54 [-0.19, 1.27]



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Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sridhar 2008	55	0.16 (1.43)	49	-0.36 (1.3)		65.9 %	0.52 [0.00, 1.04]
Subtotal (95% CI)	**79**		**72**			**100.0 %**	**0.53 [0.10, 0.95]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.42 (P = 0.016)							
4 CRQ: Mastery							
Güell 2000	24	0.935 (1.1415)	23	-0.05 (1.3812)		35.4 %	0.99 [0.26, 1.72]
Sridhar 2008	55	0.43 (1.33)	49	-0.27 (1.45)		64.6 %	0.70 [0.16, 1.24]
Subtotal (95% CI)	**79**		**72**			**100.0 %**	**0.80 [0.37, 1.23]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.64 (P = 0.00027)							

Analysis 1.9. Comparison 1 Integrated disease management versus control, Outcome 9 General health QoL: SIP mean difference.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 9 General health QoL: SIP mean difference

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SIP total							
Engstrom 1999	26	-0.07 (5.099)	24	1.02 (5.3889)		44.5 %	-1.09 [-4.00, 1.82]
Littlejohns 1991	68	-0.63 (9.2129)	65	0.4 (5.8518)		55.5 %	-1.03 [-3.64, 1.58]
Subtotal (95% CI)	**94**		**89**			**100.0 %**	**-1.06 [-3.00, 0.89]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.07 (P = 0.29)							
2 SIP: physical							
Engstrom 1999	26	0.28 (5.099)	24	1.13 (6.8586)		41.4 %	-0.85 [-4.22, 2.52]
Littlejohns 1991	68	-5.53 (7.5604)	65	-1.65 (5.9325)		58.6 %	-3.88 [-6.18, -1.58]
Subtotal (95% CI)	**94**		**89**			**100.0 %**	**-2.63 [-5.55, 0.30]**
Heterogeneity: $Tau^2 = 2.42$; $Chi^2 = 2.11$, df = 1 (P = 0.15); $I^2 = 53\%$							
Test for overall effect: Z = 1.76 (P = 0.079)							
3 SIP: psychosocial							
Engstrom 1999	26	-0.2 (6.1188)	24	0.41 (5.8788)		48.1 %	-0.61 [-3.94, 2.72]
Littlejohns 1991	68	-2.38 (11.2786)	65	-1.28 (7.1836)		51.9 %	-1.10 [-4.30, 2.10]
Subtotal (95% CI)	**94**		**89**			**100.0 %**	**-0.86 [-3.17, 1.44]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.73 (P = 0.46)							

Analysis 1.10. Comparison 1 Integrated disease management versus control, Outcome 10 Functional exercise capacity: 6MWD mean difference.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 10 Functional exercise capacity: 6MWD mean difference

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 6MWD: short-term (3 to 12 months)							
Bendstrup 1997	16	113.1 (71.2)	16	36.1 (41.6)		7.3 %	77.00 [36.59, 117.41]
Boxall 2005	23	39 (69.6)	23	4.2 (75.1)		7.2 %	34.80 [-7.05, 76.65]
Cambach 1997	12	51 (57)	7	46 (43)		6.9 %	5.00 [-40.33, 50.33]
Engstrom 1999	26	38 (90.3)	24	0.8 (101.9)		6.2 %	37.20 [-16.34, 90.74]
Fernandez 2009	27	79 (82)	14	13 (86)		6.1 %	66.00 [11.36, 120.64]
Gottlieb 2011	21	49.4 (94)	20	3.8 (81)		6.1 %	45.60 [-8.03, 99.23]
Güell 2000	30	85.067 (52.2801)	30	15.17 (60.6384)		8.3 %	69.90 [41.25, 98.55]
Güell 2006	18	63 (92)	17	-22 (72)		6.1 %	85.00 [30.43, 139.57]
Littlejohns 1991	68	-1.4 (90.89)	65	-4.9 (96.05)		8.0 %	3.50 [-28.31, 35.31]
Mendes 2010	56	81.5886 (59.6774)	29	-38.03 (59.8996)		8.5 %	119.62 [92.80, 146.45]
Theander 2009	12	40.6 (27.2)	14	16.5 (45.8)		8.3 %	24.10 [-4.40, 52.60]
van Wetering 2010	87	-1.4 (36.38)	88	-15.3 (36.59)		9.4 %	13.90 [3.09, 24.71]
Wakabayashi 2011	42	0.4 (84.4)	43	0 (103.2)		7.3 %	0.40 [-39.64, 40.44]
Wijkstra 1994	28	9 (87)	15	-28 (141)		4.4 %	37.00 [-41.29, 115.29]
Subtotal (95% CI)	**466**		**405**			**100.0 %**	**43.86 [21.83, 65.89]**
Heterogeneity: Tau² = 1307.19; Chi² = 75.79, df = 13 (P<0.00001); I² =83%							
Test for overall effect: Z = 3.90 (P = 0.000095)							
2 6MWD: long-term (> 12 months)							
Gottlieb 2011	15	-0.47 (68.9391)	17	-5.93 (45.3542)		11.4 %	5.46 [-35.55, 46.47]
van Wetering 2010	73	-15.1 (46.1376)	79	-33.4 (46.2186)		88.6 %	18.30 [3.61, 32.99]
Subtotal (95% CI)	**88**		**96**			**100.0 %**	**16.84 [3.01, 30.67]**
Heterogeneity: Tau² = 0.0; Chi² = 0.33, df = 1 (P = 0.56); I² =0.0%							
Test for overall effect: Z = 2.39 (P = 0.017)							

Analysis 1.11. Comparison 1 Integrated disease management versus control, Outcome 11 Subgroup analysis 6MWD based on type of setting.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 11 Subgroup analysis 6MWD based on type of setting

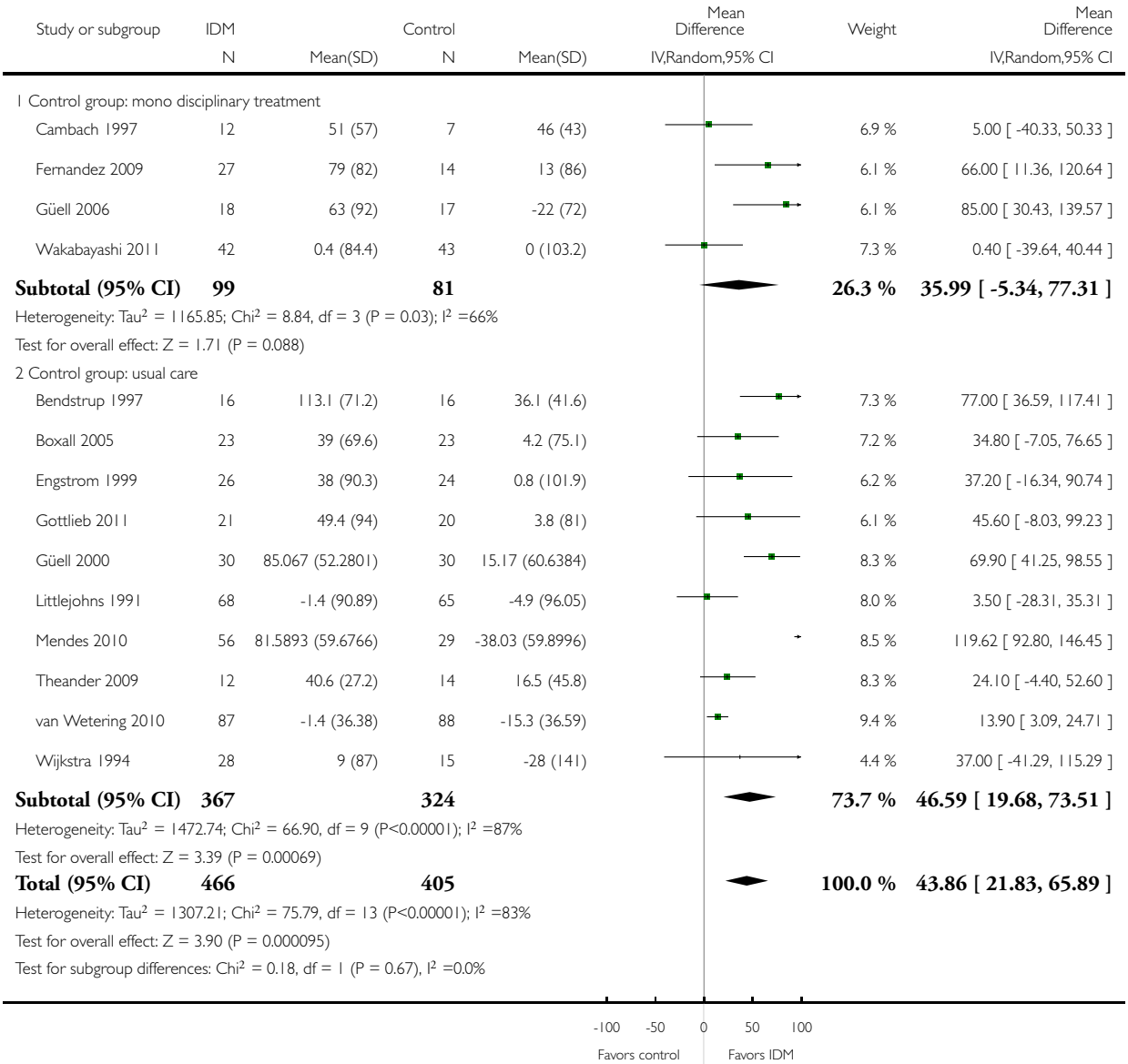
Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Primary care							
Boxall 2005	23	39 (69.6)	23	4.2 (75.1)		14.8 %	34.80 [-7.05, 76.65]
Cambach 1997	12	51 (57)	7	46 (43)		14.3 %	5.00 [-40.33, 50.33]
Fernandez 2009	27	79 (82)	14	13 (86)		13.0 %	66.00 [11.36, 120.64]
Gottlieb 2011	21	49.4 (94)	20	3.8 (81)		13.2 %	45.60 [-8.03, 99.23]
Mendes 2010	33	73.21 (50.21)	29	-38.03 (59.89)		16.6 %	111.24 [83.52, 138.96]
van Wetering 2010	87	-1.4 (36.38)	88	-15.3 (36.59)		18.1 %	13.90 [3.09, 24.71]
Wijkstra 1994	28	9 (87)	15	-28 (141)		10.0 %	37.00 [-41.29, 115.29]
Subtotal (95% CI)	**231**		**196**			**100.0 %**	**45.16 [8.65, 81.67]**
Heterogeneity: Tau^2 = 1886.99; Chi^2 = 44.58, df = 6 (P<0.00001); I^2 =87%							
Test for overall effect: Z = 2.42 (P = 0.015)							
2 Secondary care							
Bendstrup 1997	16	113.1 (71.2)	16	36.1 (41.6)		13.9 %	77.00 [36.59, 117.41]
Engstrom 1999	26	38 (90.3)	24	0.8 (101.9)		12.2 %	37.20 [-16.34, 90.74]
Güell 2000	30	85.067 (52.2801)	30	15.17 (60.6384)		15.3 %	69.90 [41.25, 98.55]
Littlejohns 1991	68	-1.4 (90.89)	65	-4.9 (96.05)		14.9 %	3.50 [-28.31, 35.31]
Mendes 2010	23	93.61 (70.57)	29	-38.03 (59.89)		14.4 %	131.64 [95.49, 167.79]
Theander 2009	12	40.6 (27.2)	14	16.5 (45.8)		15.3 %	24.10 [-4.40, 52.60]
Wakabayashi 2011	42	0.4 (84.4)	43	0 (103.2)		13.9 %	0.40 [-39.64, 40.44]
Subtotal (95% CI)	**217**		**221**			**100.0 %**	**49.18 [14.28, 84.08]**
Heterogeneity: Tau^2 = 1857.84; Chi^2 = 40.59, df = 6 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 2.76 (P = 0.0057)							
3 Tertiary care							
Güell 2006	18	63 (92)	17	-22 (72)		100.0 %	85.00 [30.43, 139.57]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**85.00 [30.43, 139.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.05 (P = 0.0023)							

Analysis 1.12. Comparison 1 Integrated disease management versus control, Outcome 12 Subgroup analysis 6MWD based on type of control group.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 12 Subgroup analysis 6MWD based on type of control group

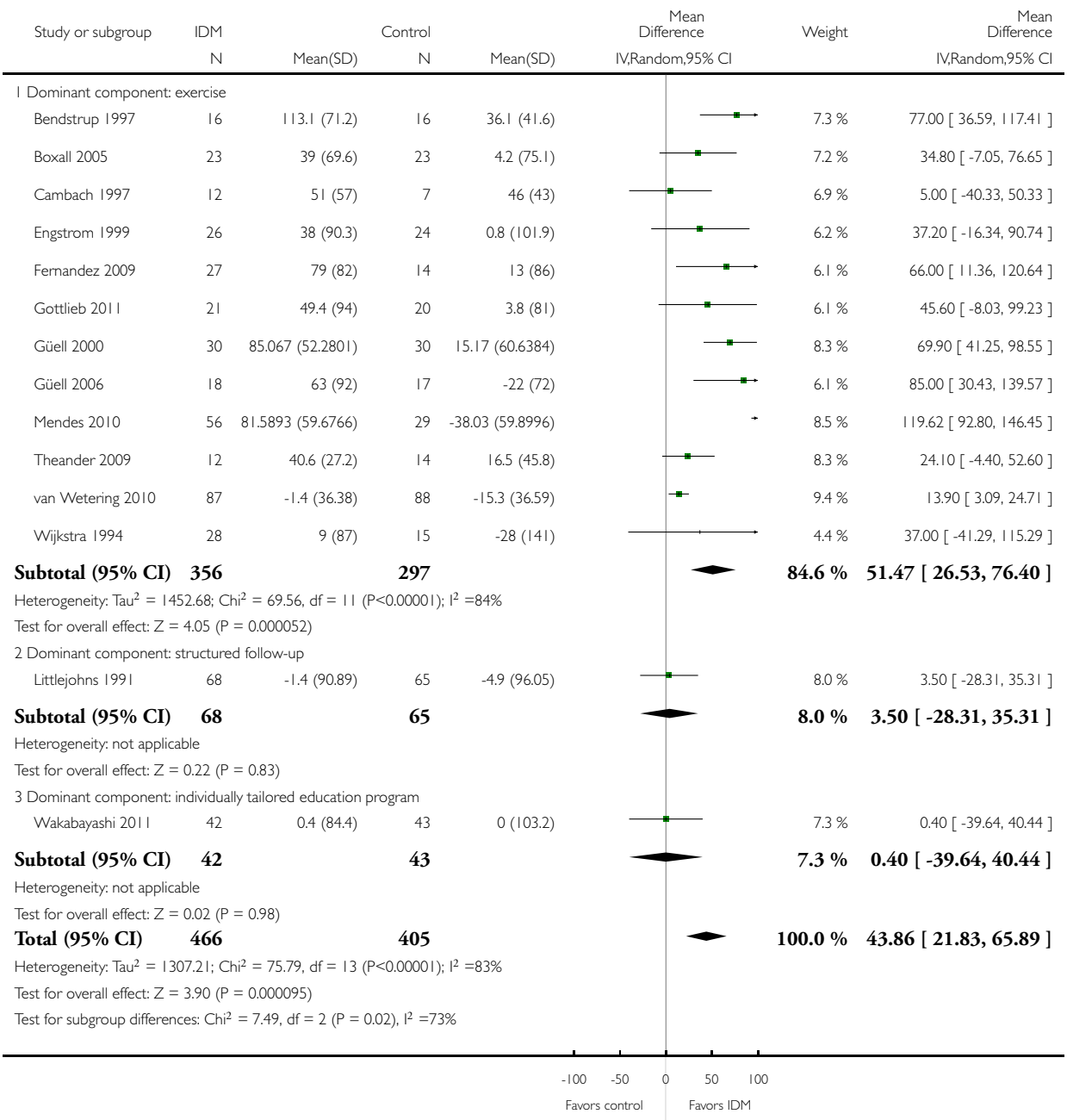


Analysis 1.13. Comparison 1 Integrated disease management versus control, Outcome 13 Subgroup analysis 6MWD based on dominant component of intervention.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 13 Subgroup analysis 6MWD based on dominant component of intervention



Analysis 1.14. Comparison 1 Integrated disease management versus control, Outcome 14 Maximal exercise capacity: cycle test (W-max).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

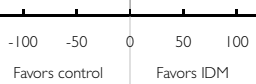
Outcome: 14 Maximal exercise capacity: cycle test (W-max)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Engstrom 1999	26	9.4 (25.5)	24	0.8 (24)		8.6 %	8.60 [-5.12, 22.32]
Strijbos 1996	15	14 (18)	15	1.3 (20)		8.8 %	12.70 [-0.92, 26.32]
van Wetering 2010	87	5.2 (14.9238)	88	-0.4 (15.9474)		77.7 %	5.60 [1.02, 10.18]
Wijkstra 1994	28	8 (31)	15	-8 (28)		4.9 %	16.00 [-2.24, 34.24]
Total (95% CI)	**156**		**142**			**100.0 %**	**6.99 [2.96, 11.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.02$, df = 3 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 3.40 (P = 0.00068)

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 Integrated disease management versus control, Outcome 15 Number of patients experiencing at least one exacerbation: short-term (3-12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 15 Number of patients experiencing at least one exacerbation: short-term (3-12 months)

Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bourbeau 2003	85/96	81/95		28.5 %	1.34 [0.57, 3.11]
Trappenburg 2011	55/103	56/113		71.5 %	1.17 [0.68, 1.99]
Total (95% CI)	**199**	**208**		**100.0 %**	**1.21 [0.77, 1.91]**

Total events: 140 (IDM), 137 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 0.83 (P = 0.40)

Test for subgroup differences: Not applicable

Analysis 1.16. Comparison 1 Integrated disease management versus control, Outcome 16 Number of patients experiencing at least one exacerbation: long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 16 Number of patients experiencing at least one exacerbation: long-term (> 12 months)

Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Sridhar 2008	53/61	53/61		31.5 %	1.00 [0.35, 2.86]
van Wetering 2010	63/89	52/90		68.5 %	1.77 [0.95, 3.29]
Total (95% CI)	**150**	**151**		**100.0 %**	**1.53 [0.90, 2.60]**

Total events: 116 (IDM), 105 (Control)

Heterogeneity: $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Integrated disease management versus control, Outcome 17 All hospital admissions: short-term (3 to 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 17 All hospital admissions: short-term (3 to 12 months)

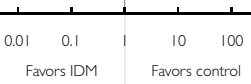
Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Littlejohns 1991	12/68	14/65		40.7 %	0.78 [0.33, 1.84]
Rea 2004	29/82	26/51		59.3 %	0.53 [0.26, 1.07]
Total (95% CI)	**150**	**116**		**100.0 %**	**0.62 [0.36, 1.07]**

Total events: 41 (IDM), 40 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.72 (P = 0.085)

Test for subgroup differences: Not applicable

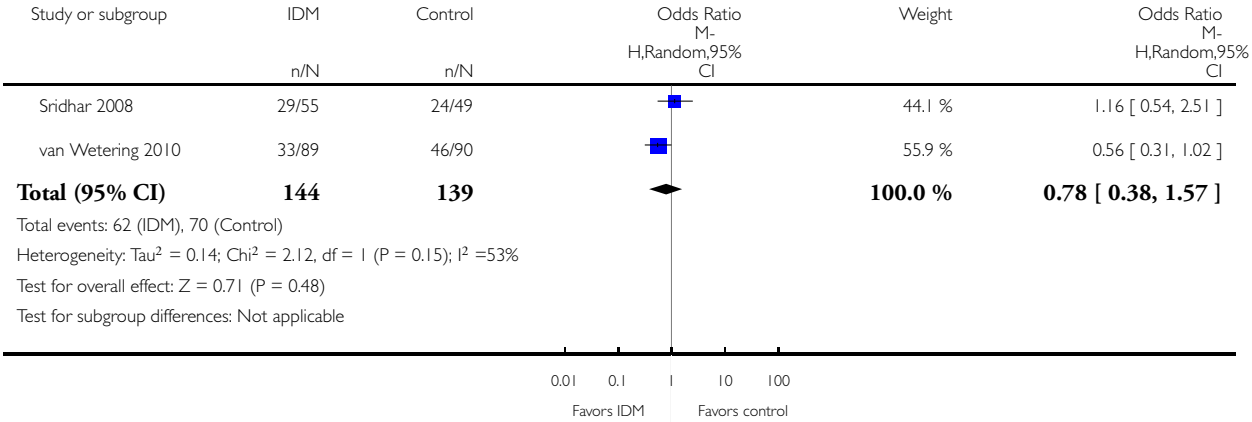


Analysis 1.18. Comparison 1 Integrated disease management versus control, Outcome 18 All hospital admissions: long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 18 All hospital admissions: long-term (> 12 months)



Analysis 1.19. Comparison 1 Integrated disease management versus control, Outcome 19 Respiratory-related hospital admissions: short-term (3 to 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 19 Respiratory-related hospital admissions: short-term (3 to 12 months)

Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bourbeau 2003	31/96	48/95		21.2 %	0.47 [0.26, 0.84]
Boxall 2005	5/23	5/23		6.1 %	1.00 [0.25, 4.06]
Koff 2009	1/19	3/19		2.3 %	0.30 [0.03, 3.14]
Rea 2004	18/82	20/51		15.4 %	0.44 [0.20, 0.94]
Rice 2010	62/372	86/371		31.5 %	0.66 [0.46, 0.95]
Smith 1999	33/47	25/45		13.2 %	1.89 [0.80, 4.45]
Trappenburg 2011	7/109	9/118		10.2 %	0.83 [0.30, 2.31]
Total (95% CI)	**748**	**722**		**100.0 %**	**0.68 [0.47, 0.99]**

Total events: 157 (IDM), 196 (Control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.18$, df = 6 (P = 0.16); $I^2 = 35\%$

Test for overall effect: Z = 2.02 (P = 0.043)

Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 Integrated disease management versus control, Outcome 20 Respiratory-related hospital admissions: long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 20 Respiratory-related hospital admissions: long-term (> 12 months)

Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
van Wetering 2010	15/89	23/90		100.0 %	0.59 [0.28, 1.22]
Total (95% CI)	**89**	**90**		**100.0 %**	**0.59 [0.28, 1.22]**

Total events: 15 (IDM), 23 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Integrated disease management versus control, Outcome 21 Hospital days per patient (all causes): short-term (3 to 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

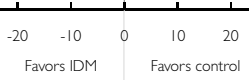
Outcome: 21 Hospital days per patient (all causes): short-term (3 to 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bourbeau 2003	96	7.2 (19.5)	95	12.5 (21.2)		9.7 %	-5.30 [-11.08, 0.48]
Boxall 2005	23	5.6 (2.96)	23	8.8 (4.71)		25.4 %	-3.20 [-5.47, -0.93]
Engstrom 1999	26	4.9 (13.77)	24	1.6 (8.33)		8.7 %	3.30 [-2.95, 9.55]
Farrero 2001	46	7.43 (15.6)	48	18.2 (24.55)		5.5 %	-10.77 [-19.05, -2.49]
Rea 2004	82	1.1 (7.8)	51	4 (7.8)		22.5 %	-2.90 [-5.63, -0.17]
Trappenburg 2011	109	6.6 (2.8)	118	11.9 (9.8)		28.2 %	-5.30 [-7.14, -3.46]
Total (95% CI)	**382**		**359**			**100.0 %**	**-3.78 [-5.90, -1.67]**

Heterogeneity: $Tau^2 = 3.22$; $Chi^2 = 11.00$, df = 5 (P = 0.05); $I^2 = 55\%$

Test for overall effect: Z = 3.51 (P = 0.00044)

Test for subgroup differences: Not applicable



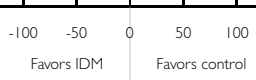
Analysis 1.22. Comparison 1 Integrated disease management versus control, Outcome 22 Hospital days per patient: long-term (> 12 months).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 22 Hospital days per patient: long-term (> 12 months)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
van Wetering 2010	87	4.9 (14)	88	4.3 (10)		0.60 [-3.01, 4.21]



Analysis 1.23. Comparison 1 Integrated disease management versus control, Outcome 23 ED visits.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 23 ED visits

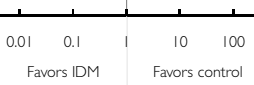
Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bourbeau 2003	39/96	60/95		29.6 %	0.40 [0.22, 0.71]
Rea 2004	5/83	7/52		16.9 %	0.41 [0.12, 1.37]
Rice 2010	51/372	85/371		34.1 %	0.53 [0.36, 0.78]
Smith 1999	14/47	6/45		19.3 %	2.76 [0.95, 7.98]
Total (95% CI)	**598**	**563**		**100.0 %**	**0.64 [0.33, 1.25]**

Total events: 109 (IDM), 158 (Control)

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 10.26$, df = 3 (P = 0.02); $I^2 = 71\%$

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1 Integrated disease management versus control, Outcome 24 Number of patients using at least one course of oral steroids.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 24 Number of patients using at least one course of oral steroids

Study or subgroup	IDM n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Farrero 2001	20/60	27/62		34.0 %	0.65 [0.31, 1.35]
Littlejohns 1991	33/68	24/65		36.3 %	1.61 [0.81, 3.22]
Rea 2004	31/52	21/41		29.6 %	1.41 [0.62, 3.21]
Total (95% CI)	**180**	**168**		**100.0 %**	**1.13 [0.64, 2.01]**

Total events: 84 (IDM), 72 (Control)

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 3.47$, df = 2 (P = 0.18); $I^2 = 42\%$

Test for overall effect: Z = 0.44 (P = 0.66)

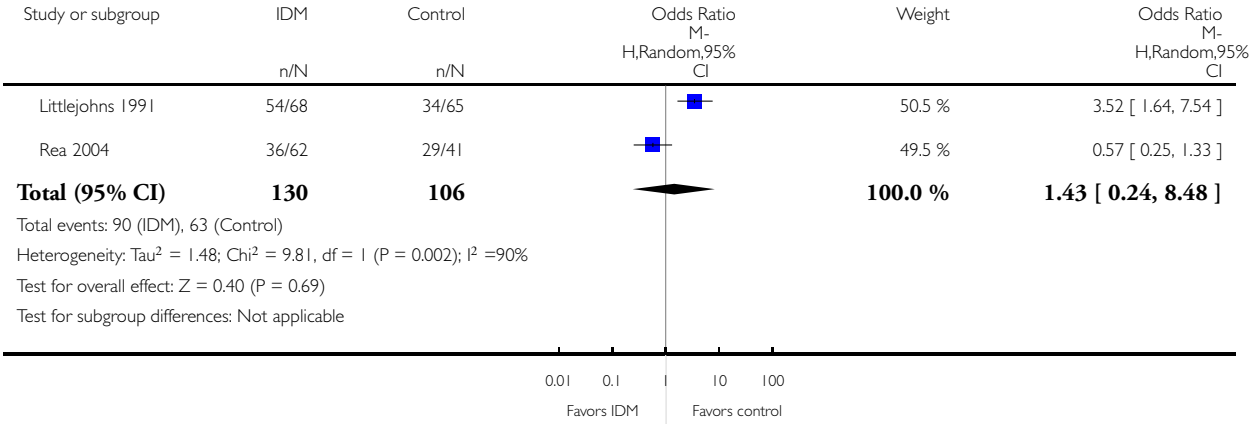
Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 Integrated disease management versus control, Outcome 25 Number of patients using at least one course of antibiotics.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 25 Number of patients using at least one course of antibiotics



Analysis 1.26. Comparison 1 Integrated disease management versus control, Outcome 26 MRC dyspnea score.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 26 MRC dyspnea score

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mendes 2010	56	-0.8929 (0.9663)	29	-0.66 (0.9738)		17.1 %	-0.24 [-0.67, 0.20]
van Wetering 2010	87	-0.3 (0.9327)	88	0.1 (0.9381)		42.3 %	-0.40 [-0.68, -0.12]
Wakabayashi 2011	42	-0.2 (0.9324)	43	0.01 (0.0736)		40.6 %	-0.21 [-0.49, 0.07]
Total (95% CI)	**185**		**160**			**100.0 %**	**-0.30 [-0.48, -0.11]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 3.21 (P = 0.0013)

Test for subgroup differences: Not applicable

Analysis 1.27. Comparison 1 Integrated disease management versus control, Outcome 27 Borg score.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 27 Borg score

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Boxall 2005	23	-0.13 (1.3)	23	0.22 (1.4)		48.7 %	-0.35 [-1.13, 0.43]
Gottlieb 2011	19	0.3 (2.4)	20	-0.7 (1.4)		29.7 %	1.00 [-0.24, 2.24]
Güell 2000	30	0.166 (2.9084)	30	0.1 (3.2754)		21.5 %	0.07 [-1.50, 1.63]
Total (95% CI)	**72**		**73**			**100.0 %**	**0.14 [-0.70, 0.98]**

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 3.26$, df = 2 (P = 0.20); $I^2 = 39\%$

Test for overall effect: Z = 0.33 (P = 0.74)

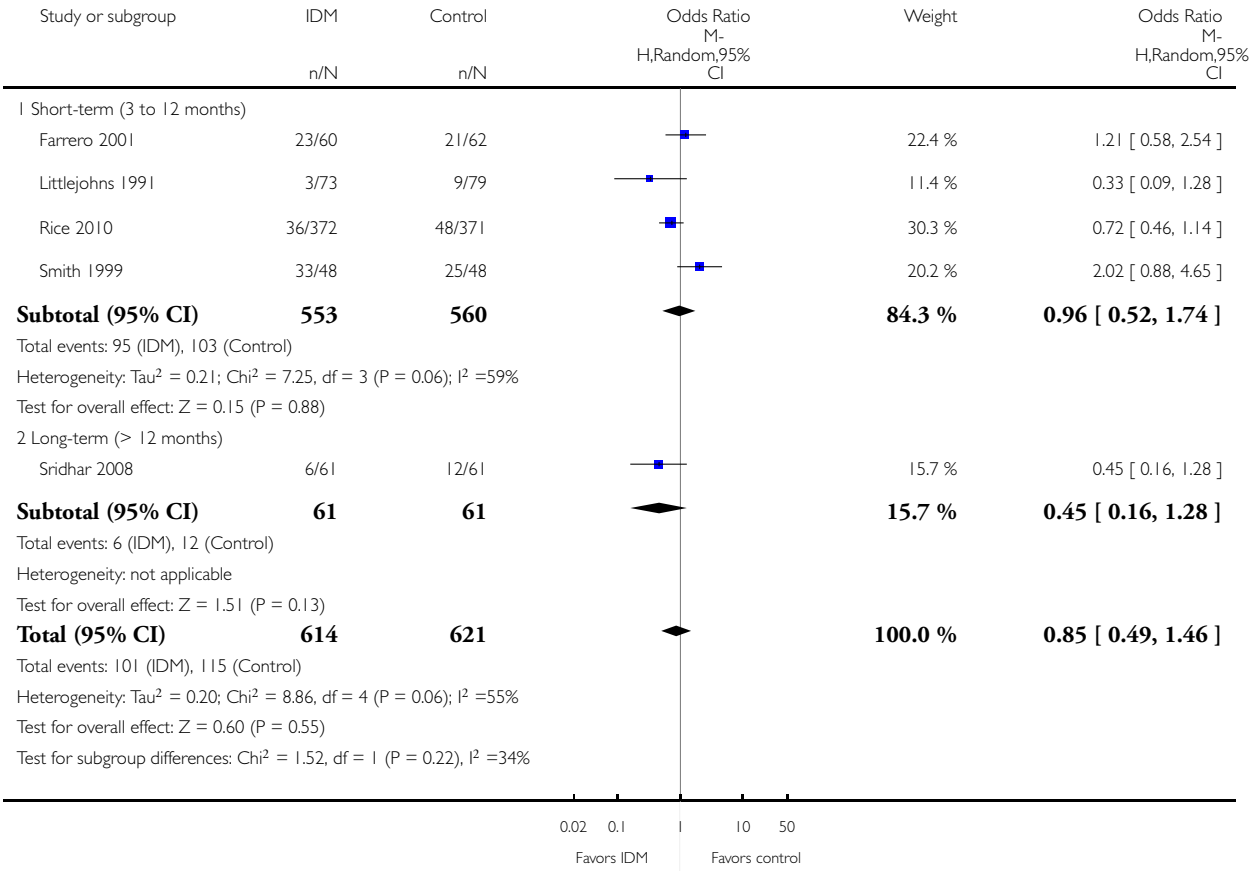
Test for subgroup differences: Not applicable

Analysis 1.28. Comparison 1 Integrated disease management versus control, Outcome 28 Mortality.

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 28 Mortality

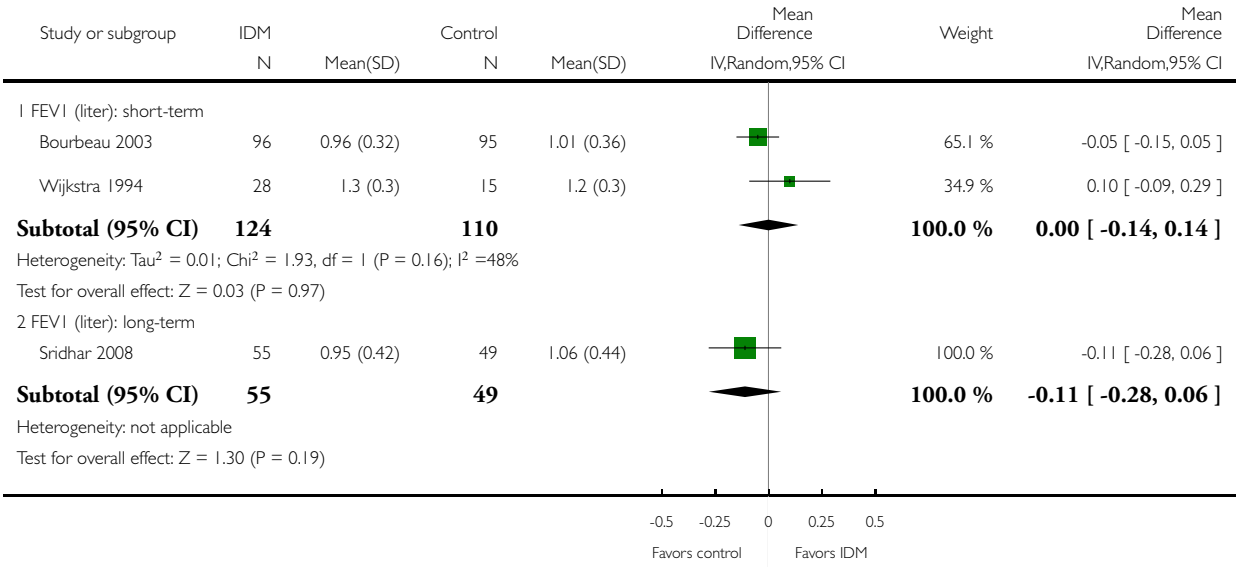


Analysis 1.29. Comparison 1 Integrated disease management versus control, Outcome 29 FEV1 (liter).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 29 FEV1 (liter)



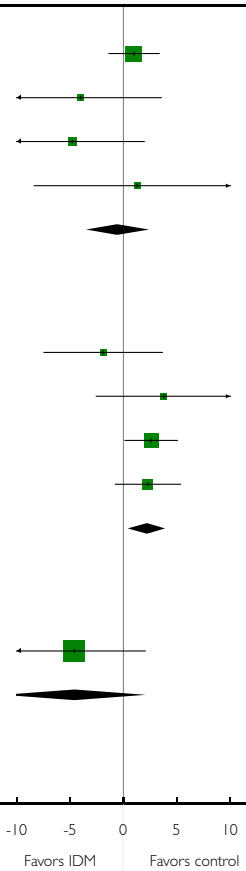
Analysis 1.30. Comparison 1 Integrated disease management versus control, Outcome 30 FEV1 (% predicted).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 30 FEV1 (% predicted)

Study or subgroup	IDM N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 FEV1 (% predicted): short-term							
Farrero 2001	46	25 (6)	48	24 (6)		62.0 %	1.00 [-1.43, 3.43]
Fernandez 2009	27	34 (13)	14	38 (11)		13.4 %	-4.00 [-11.57, 3.57]
Güell 2000	30	33.5 (12.01)	30	38.3 (14.8)		16.0 %	-4.80 [-11.62, 2.02]
Wakabayashi 2011	42	62.1 (19.9)	43	60.8 (25.3)		8.6 %	1.30 [-8.36, 10.96]
Subtotal (95% CI)	**145**		**135**			**100.0 %**	**-0.57 [-3.54, 2.39]**
Heterogeneity: Tau² = 2.16; Chi² = 3.70, df = 3 (P = 0.30); I² =19%							
Test for overall effect: Z = 0.38 (P = 0.70)							
2 FEV1 (% predicted; mean change): short-term							
Littlejohns 1991	68	-2.06 (11.36)	65	-0.15 (19.98)		10.1 %	-1.91 [-7.47, 3.65]
Mendes 2010	56	13.74 (13.37)	29	9.91 (14.95)		7.5 %	3.83 [-2.64, 10.30]
van Wetering 2010	87	0.87 (6.72)	88	-1.74 (9.76)		50.7 %	2.61 [0.13, 5.09]
Wood-Baker 2006	60	0.5 (10.2)	61	-1.8 (7.1)		31.7 %	2.30 [-0.84, 5.44]
Subtotal (95% CI)	**271**		**243**			**100.0 %**	**2.15 [0.38, 3.91]**
Heterogeneity: Tau² = 0.0; Chi² = 2.45, df = 3 (P = 0.48); I² =0.0%							
Test for overall effect: Z = 2.38 (P = 0.017)							
3 FEV1 (% predicted): long-term							
Sridhar 2008	55	41.1 (17.1)	49	45.7 (17.48)		100.0 %	-4.60 [-11.26, 2.06]
Subtotal (95% CI)	**55**		**49**			**100.0 %**	**-4.60 [-11.26, 2.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							

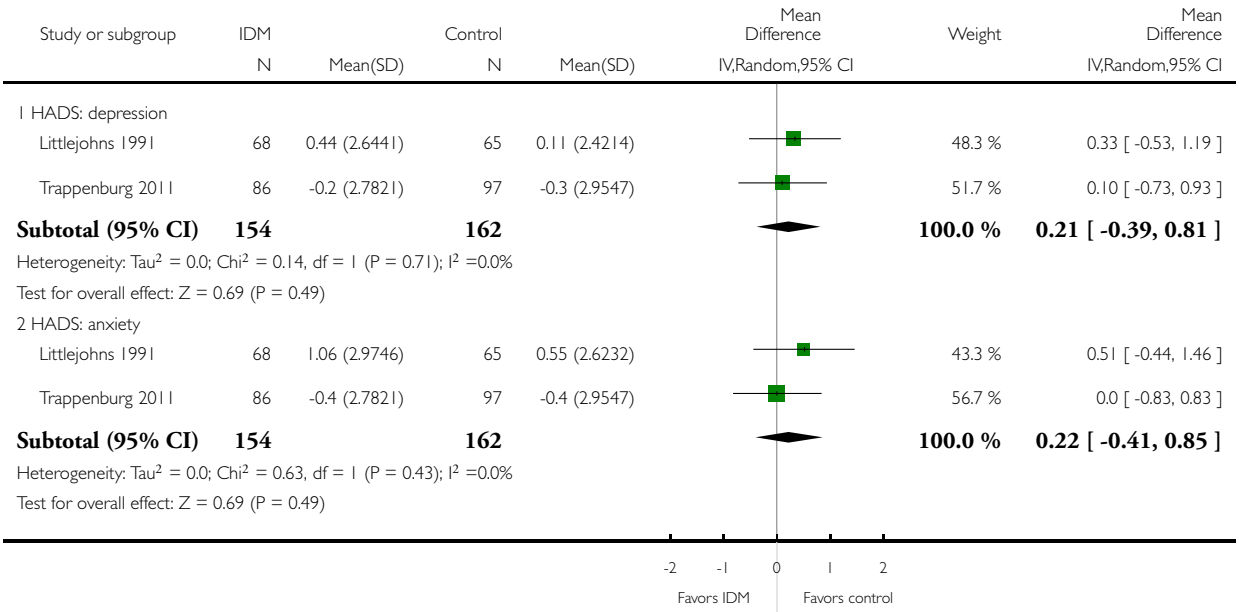


Analysis 1.31. Comparison 1 Integrated disease management versus control, Outcome 31 Anxiety and depression (HADS).

Review: Integrated disease management interventions for patients with chronic obstructive pulmonary disease

Comparison: 1 Integrated disease management versus control

Outcome: 31 Anxiety and depression (HADS)



ADDITIONAL TABLES

Table 1. Characteristics of included studies

Study	Country	N (randomised)	N (completed)	Number of components intervention	Number of health care providers	Main component intervention	Setting	Control group
Aiken 2006	US	41	18	5	2	SF	PRIM	U
Bendstrup 1997	Denmark	42	32	4	7	E	SEC	U
Bourbeau 2003	Canada	191	165	4	4	SM	SEC	U
Boxall 2005	Australia	60	46	2	3	E	PRIM	U

Table 1. Characteristics of included studies (*Continued*)

Cambach 1997	Netherlands	43	23	2	2	E	PRIM	DRUG
Dheda 2004	UK	33	25	4	2	SF	SEC	U
Engstrom 1999	Sweden	55	50	4	5	E	SEC	U
Farrero 2001	Spain	122	94	2	2	SF	SEC	U
Fernandez 2009	Spain	50	41	2	2	E	PRIM	EDU
Gottlieb 2011	Denmark	61	26	4	Multidisciplinary team, not specified	E	PRIM	U
Güell 2000	Spain	60	47	3	3	E	SEC	U
Güell 2006	Spain	40	25	2	4	E	TERT	DRUG
Koff 2009	US	40	38	4	2	SM	PRIM	U
Littlejohns 1991	UK	152	133	4	3	SF	SEC	U
Mendes 2010	Brazil	117	85	2	2	E	PRIM/SEC	U
Rea 2004	New Zealand	135	117	5	4	SM/SF	PRIM/SEC	U
Rice 2010	US	743	743	3	2	SM	SEC	EDU
Smith 1999	Australia	96	36	8	3	SF	PRIM/SEC	U
Sridhar 2008	UK	122	104	4	3	E/SM	PRIM/SEC	U
Strijbos 1996	Netherlands	50	41	3	3	E	PRIM/SEC	U
Theander 2009	Sweden	30	26	4	4	E	SEC	U
Trappenburg	Netherlands	233	193	3	3	SM	SEC	U

Table 1. Characteristics of included studies (*Continued*)

Wakabayashi 2011	Japan	102	85	4	2	IT EDU	SEC	EDU
Wetering 2010	Netherlands	199	175	4	3	E	SEC	U
Wijkstra 1995	Netherlands	45	43	2	3	E	PRIM	U
Wood-Baker 2006	Australia	135	112	3	2	SM	PRIM	EDU

Main component: SF: structural follow-up; SM: self management; E: exercise; IT EDU: individually tailored education
Setting: PRIM: primary care; SEC: secondary care; TERT: tertiary care
Control group: U: usual care; DRUG: optimization of drug treatment; EDU: education

Table 2. Components of IDM in each included study

Author	Education	Self management	Exacerbation/ action plan	Exercise	Psychosocial/ occupational	Smoking	Optimal medication	Nutrition	Follow-up	Case management	Multidisciplinary
Aiken 2006	x	x	x				x			x	
Bendstrup 1997	x			x	x	x					
Bourbeau 2003	x		x	x					x		
Boxall 2005	x			x							
Cambach 1997	x			x							
Dheda 2004	x				x		x		x		
Engstrom	x			x	x			x			

Table 2. Components of IDM in each included study (*Continued*)

1999											
Farrero 2001									x	x	
Fernandez	x			x							
Gottlieb 2011	x			x		x		x			
Güell 2000	x			x					x		
Güell 2006	x			x							
Koff 2009	x	x	x						x		
Littlejohns 1991	x						x		x	x	
Mendes 2010	x			x							
Rea 2004	x		x	x					x		x
Rice 2010	x	x	x								
Smith 1999	x	x	x	x		x	x			x	x
Sridhar 2008	x		x	x					x		
Strijbos 1996	x			x					x		
Theander 2009	x			x	x			x			
Trappenburg 2011	x	x	x								

Table 2. Components of IDM in each included study (*Continued*)

Wakabayashi 2011	x	x	x			x					
Wetering 2010	x			x		x		x			
Wijkstra 1995	x			x							
Wood-Baker 2006	x	x	x								

APPENDICES

Appendix 1. MEDLINE search strategy

1. Pulmonary Disease, Chronic Obstructive/
2. COPD.mp.
3. Chronic Obstructive Pulmonary Disease.mp.
4. Chronic Obstructive Airway Disease.mp.
5. Chronic Obstructive Lung Disease.mp.
6. pulmonary emphysema.mp.
7. chronic bronchitis.mp.
8. COAD.mp.
9. Chronic Airflow Obstruction.mp.
10. or/1-9
11. disease management/
12. Disease management.mp.
13. exp Managed Care Programs/
14. managed care.mp.
15. (insurance and "case management").mp.
16. exp Patient Care Planning/
17. "patient care plan$".mp.
18. "nursing care plan$".mp.
19. "goals of care".mp.
20. "care goal".mp.
21. exp "Delivery of Health Care, Integrated"/
22. (integrated and (health$ or care$ or delivery or system$)).mp.
23. disease state management.mp.
24. Comprehensive Health Care/
25. "comprehensive health care".mp.
26. ((interdisciplin$ or multidisciplin$) and (care or health$ or delivery or system$)).mp.
27. Primary Nursing/

28. “primary nursing”.mp.
29. “community based”.mp.
30. Patient-Centered Care/
31. Patient Care Management/
32. (patient adj3 (care or management)).mp.
33. practice guideline/
34. education, medical, continuing/ or education, nursing, continuing/
35. exp community health services/
36. Primary Health Care/
37. “patient care team”.mp.
38. “critical pathways”.mp.
39. “case management”.mp.
40. Self Care/
41. (continuity adj3 “patient care”).mp.
42. guideline$.mp.
43. “clinical protocol”.mp.
44. “patient education”.mp.
45. (self-care or “self care”).mp.
46. reminder systems.mp. or Reminder Systems/
47. Health Education/
48. Health Promotion/
49. (health adj3 (education or promotion)).mp.
50. Community Health Planning/
51. ambulatory care.mp.
52. feedback.mp.
53. or/11-52
54. 10 and 53
55. (clinical trial or controlled clinical trial or randomised controlled trial).pt.
56. (randomised or randomised).ab,ti.
57. placebo.ab,ti.
58. dt.fs.
59. randomly.ab,ti.
60. trial.ab,ti.
61. groups.ab,ti.
62. or/55-61
63. Animals/
64. Humans/
65. 63 not (63 and 64)
66. 62 not 65
67. 54 and 66
[Limited to pub. Date > = 1990]

Appendix 2. EMBASE search strategy

1. chronic obstructive lung disease/
2. COPD.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
3. Chronic Obstructive Pulmonary Disease.mp.
4. Chronic Obstructive Airway Disease.mp.
5. Chronic Obstructive Lung Disease.mp.
6. pulmonary emphysema.mp.
7. chronic bronchitis.mp.
8. COAD.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
9. Chronic Airflow Obstruction.mp.
10. or/1-9
11. disease management/
12. Disease management.mp.
13. managed care/
14. managed care.mp.
15. (insurance and "case management").mp.
16. patient care planning/
17. "patient care plan$".mp.
18. "nursing care plan$".mp.
19. "goals of care".mp.
20. "care goal".mp.
21. integrated health care system/
22. (integrated adj5 (health$ or care$ or delivery or system$)).mp.
23. disease state management.mp.
24. health care/
25. "comprehensive health care".mp.
26. ((interdisciplin$ or multidisciplin$) adj5 (care or health$ or delivery or system$)).mp.
27. primary nursing/
28. "primary nursing".mp.
29. "community based".mp.
30. patient care/
31. (patient adj3 (care or management)).mp.
32. practice guideline/
33. medical education/
34. exp community care/
35. primary health care/
36. "patient care team".mp.
37. "critical pathways".mp.
38. "case management".mp.
39. self care/
40. (continuity adj3 "patient care").mp.
41. guideline$.mp.
42. "clinical protocol".mp.
43. "patient education".mp.
44. (self-care or "self care").mp.
45. reminder system/
46. reminder systems.mp.
47. health education/
48. health promotion/
49. (health adj3 (education or promotion)).mp.

50. health care planning/
51. ambulatory care.mp.
52. feedback.mp.
53. or/11-52
54. 10 and 53
55. Randomized Controlled Trial/
56. randomisation/
57. Controlled Study/
58. Clinical Trial/
59. controlled clinical trial/
60. Double Blind Procedure/
61. Single Blind Procedure/
62. Crossover Procedure/
63. or/55-62
64. (clinica$ adj3 trial$).mp.
65. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).mp.
66. exp Placebo/
67. placebo$.mp.
68. random$.mp.
69. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).mp.
70. (crossover$ or cross-over$).mp.
71. or/64-70
72. 63 or 71
73. exp ANIMAL/
74. Nonhuman/
75. Human/
76. 73 or 74
77. 76 not 75
78. 72 not 77
79. 54 and 78
[Limited to pub. Date >=1990]

Appendix 3. CINAHL search strategy

S1 (MH "Pulmonary Disease, Chronic Obstructive+")
S2 COPD
S3 "chronic Obstructive Pulmonary Disease"
S4 "Chronic Obstructive Airway Disease"
S5 "Chronic Obstructive Lung Disease"
S6 "pulmonary emphysema"
S7 "chronic bronchitis"
S8 COAD
S9 "Chronic Airflow Obstruction"
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S11 (MH "Disease Management")
S12 "Disease management"
S13 (MH "Managed Care Programs+")
S14 "managed care"
S15 insurance and "case management"
S16 (MH "Patient Care Plans+")
S17 "patient care plan*"
S18 "nursing care plan*"

S19 "goals of care"
S20 "care goal"
S21 (MH "Health Care Delivery, Integrated")
S22 (integrated and (health* or care* or delivery or system*))
S23 "disease state management"
S24 "Comprehensive Health Care"
S25 ((interdisciplin* or multidisciplin*) and (care or health* or delivery or system*))
S26 (MH "Primary Nursing")
S27 "primary nursing"
S28 "community based"
S29 (MH "Patient Centered Care")
S30 "patient care"
S31 "patient management"
S32 (MH "Education, Medical, Continuing")
S33 Education, Nursing, Continuing
S34 (MH "Community Health Services+")
S35 (MH "Primary Health Care")
S36 "patient care team"
S37 (MH "Critical Path")
S38 "case management"
S39 (MH "Self Care")
S40 (MH "Continuity of Patient Care")
S41 guideline*
S42 "clinical protocol"
S43 "patient education"
S44 self-care or "self care"
S45 (MH "Reminder Systems")
S46 "reminder system*"
S47 (MH "Health Education")
S48 (MH "Health Promotion+")
S49 (health N3 educat*) or (health N3 promot*)
S50 "Community Health Planning"
S51 "ambulatory care"
S52 feedback
S53 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52
S54 S10 and S53
S55 (DE "RANDOMIZED CONTROLLED TRIALS")
S56 (MH "Double-Blind Studies")
S57 (MH "Random Assignment")
S58 (MH "Placebos")
S59 placebo*
S60 random*
S61 crossover* or cross-over*
S62 clinical* and (trial* or study or studies)
S63 (single* or double* or triple*) and blind*
S64 S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63
S65 S54 and S64 [Limiters - Exclude MEDLINE records; Published Date from: 19900101-20111231]

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees
#2 COPD
#3 "chronic Obstructive Pulmonary Disease"
#4 "Chronic Obstructive Airway Disease"
#5 "Chronic Obstructive Lung Disease"
#6 "pulmonary emphysema"
#7 "chronic bronchitis"
#8 COAD
#9 "Chronic Airflow Obstruction"
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Disease Management, this term only
#12 "Disease management"
#13 MeSH descriptor Managed Care Programs explode all trees
#14 "managed care"
#15 insurance and "case management"
#16 MeSH descriptor Patient Care Planning explode all trees
#17 "patient care plan*"
#18 "nursing care plan*"
#19 "goals of care"
#20 "care goal"
#21 MeSH descriptor Delivery of Health Care, Integrated explode all trees
#22 (integrated and (health* or care* or delivery or system*))
#23 "disease state management"
#24 MeSH descriptor Comprehensive Health Care, this term only
#25 "comprehensive health care"
#26 ((interdisciplin* or multidisciplin*) and (care or health* or delivery or system*))
#27 MeSH descriptor Primary Nursing, this term only
#28 "primary nursing"
#29 "community based"
#30 MeSH descriptor Patient-Centered Care explode all trees
#31 MeSH descriptor Patient Care Management, this term only
#32 "patient care"
#33 "patient management"
#34 MeSH descriptor Education, Medical, Continuing, this term only
#35 MeSH descriptor Education, Nursing, Continuing, this term only
#36 MeSH descriptor Community Health Services explode all trees
#37 MeSH descriptor Primary Health Care, this term only
#38 "patient care team"
#39 "critical pathways"
#40 "case management"
#41 MeSH descriptor Self Care, this term only
#42 continuity NEAR/3 "patient care"
#43 guideline*
#44 "clinical protocol"
#45 "patient education"
#46 self-care or "self care"
#47 MeSH descriptor Reminder Systems explode all trees
#48 "reminder system*"
#49 MeSH descriptor Health Education, this term only
#50 MeSH descriptor Health Promotion explode all trees
#51 health NEAR/3 (educat* or promot*)

#52 MeSH descriptor Community Health Planning, this term only
#53 "ambulatory care"
#54 feedback
#55 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54)
#56 (#55 AND #10)
#57 (#56), from 1990 to 2013

Appendix 5. Cochrane Airways Group Register search strategy

#45=COPD
AND
("disease management" or "managed care" or insurance* or "case management" or "care plan" or (goal* and care) or (integrat* and (system* or delivery or care or health*)) or (comprehensive and "health care") or ((interdisciplin* or multidisciplin*) and (care or health* or delivery or system*)) or "primary nursing" or patient-cent* or "patient care" or "patient manag*" or "practice guideline*" or "community health" or "primary health care" or "critical pathway*" or self-care or "self care" or "clinical protocol*" or "patient educat*" or reminder* or (health and (educat* or promot*)) or ((community or health) and plan*) or "ambulatory care" or feedback)
[Limited to pub. date>=1990]

CONTRIBUTIONS OF AUTHORS

AK, NC and NS wrote the protocol.

All authors contributed to and approved the protocol.

AK, NS and NC selected trials.

AK and NC extracted data and assessed risk of bias.

AK was responsible for data management in RevMan.

All authors contributed to and approved the final version of the review.

DECLARATIONS OF INTEREST

AK, NC, WA, JG, MB and MR are part of the ongoing RECODE trial, which investigates the cost-effectiveness of integrated care in primary care COPD patients in a cluster-randomized controlled trial. The Leiden University Medical Centre received a grant from ZonMW (Dutch governmental agency) for the RECODE trial and the Erasmus University (iMTA) received additional financial support from Achmea (Dutch Healthcare Insurer) for the economic evaluation of the intervention in the RECODE trial. In the future, our RCT will be included in this Cochrane Review.

MR is involved in cost-effectiveness studies of various COPD interventions, both pharmacological and non-pharmacological. She was the project leader of the cost-effectiveness study of the INTERCOM trial, a trial that will be included in this review.

NC is a senior researcher in the field of integrated disease management programs and involved in several initiatives promoting education, developing software applications and providing e-health solutions, which may be considered as a potential conflict of interest.

NS: none known.

SOURCES OF SUPPORT

Internal sources

- LUMC, Leiden, Netherlands.

Leiden University Medical Centre

- iMTA, Rotterdam, Netherlands.

Institute for Medical Technology Assessment

External sources

- ZonMW, Netherlands.

The Netherlands Organisation for Health Research and Development

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added Borg score next to the MRC Dyspnea Score as an instrument to measure dyspnoea under 'Secondary outcomes'.

We did not search the DARE database for non-Cochrane reviews.

INDEX TERMS

Medical Subject Headings (MeSH)

*Disease Management; *Quality of Life; Delivery of Health Care, Integrated [*methods]; Exercise Tolerance; Hospitalization [statistics & numerical data]; Patient Care Team; Pulmonary Disease, Chronic Obstructive [physiopathology; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male